

ORGANIC CHEMISTRY

WITH APPLICATIONS TO PHARMACY
AND MEDICINE

BY

ELDIN V. LYNN, Ph.D.

PROFESSOR OF CHEMISTRY, MASSACHUSETTS COLLEGE OF PHARMACY, BOSTON

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PREFACE TO SECOND EDITION

THE newer revisions of the Pharmacopœia and Formulary and the introduction of many new compounds into therapy have made necessary some changes in the text. In general, however, the author has seen no need for making any extensive alteration in arrangement; the many favorable comments that have been received on this arrangement and experience in using it with classes over the past several years seem to warrant retention of the general order.

The author is deeply grateful for the many friendly criticisms that he has received during the past three years. He sincerely hopes that this revision will have satisfactorily corrected the errors previously found and will have eliminated those points that might have been called mistakes in judgment.

E. V. L.

BOSTON, MASSACHUSETTS

PREFACE TO FIRST EDITION

For several years the writer has felt a serious need for a good texhook in organic chemistry, that would also give the medical and pharmaceutical applications. Where it is necessary to present all of this in one course, the teacher at present is almost compelled to employ one of the numerous texts in the fundamentals and to supplement this by discussion of the official substances in lectures. No matter how efficient such a method is, the applications are generally missed by the student. Even in those schools in which students come to the professional faculty with a primary course already completed, the teacher must feel the need for a textbook that would review the basic reactions and apply them to the substances used in medicine and pharmacy.

The present volume was written in an attempt to fill such a need. The aim has been to give an adequate discussion to the important principles of modern organic chemistry and to bring in for purposes of illustration those compounds that are used in pharmaceutical and medical practice. If the available time is sufficient, the material can be presented in one course, but the text should be equally of value for a course in pharmaceutical organic chemistry where the student has previously studied the general subject.

In developing the subject, the chief departure from usual methods consists in maintaining throughout the general point of view. The total number of compounds that have been encountered is truly stupendous, and we cannot hope to learn more than reactions that are common to large groups. Any attempt to teach chemicals in place of chemistry, in a relatively short time, is almost certain to be a failure. It would seem reasonable that the best approach must involve a thorough presentation of general principles and properties.

The writer is indebted to his colleagues for much helpful advice and also to the various textbooks that have been freely consulted. He would appreciate criticisms and suggestions from teachers or students or from anyone else who might use the book.

E. V. L.

BOSTON, MASSACHUSETTS

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ORGANIC CHEMISTRY

CHAPTER I

INTRODUCTION

THE student has undoubtedly been impressed by the fact that many familiar substances have been ignored in his early study of chemistry. Perhaps the teacher has pointed out some reason for omitting any discussion of such compounds as sugar, alcohol, glycerin, camphor, and ether. In any event, the consideration of these and many other substances containing carbon is usually postponed until the student has become familiar with the fundamental principles of chemistry and has learned about the compounds of other elements.

The main reason for this separation of carbonaceous matter from those compounds which contain no carbon is a custom brought about by erroneous ideas in the early stages of the science. Up to the beginning of the nineteenth century chemists had been able to make all sorts of compounds from the elements; but those which occurred naturally in plants and animals, and which were apparently quite different in most properties, were considered as being formed by some mysterious, vital force and as being beyond human power to manufacture. It is true that many of these substances had been isolated and studied and that a few, like oxalic acid, had been actually made from natural materials, but no one had yet built up, or synthesized, any from the elements. Beginning with the production of urea by Wöhler, in 1828, this older idea was gradually and somewhat reluctantly abandoned and today we are able to manufacture thousands of these compounds of carbon with very little trouble. In the meantime, however, the distinctive conception of organic (life) and inorganic (mineral) chemistry had taken deep hold and we still make such a separation, in spite of our knowledge that the original reason for such differentiation is not tenable.

There are several other cogent arguments for maintaining the present system. In the first place, while the known number of inorganic compounds is about 30,000, our list of organic compounds has increased rapidly during the last century to probably more than 400,000, and it is being added to at a rate which now amounts to several thousand a year.

Secondly, the properties and reactions are usually different in a notable degree. While the inorganic compounds are not generally soluble in alcohol, ether, etc., the organic compounds frequently dissolve in these agents. Most of the carbon compounds melt at a much lower temperature and all of them burn readily to carbon dioxide. With few exceptions, they are relatively unstable to many common conditions, such as changes in temperature, treatment with other forms of energy, and admixture with one or more of a variety of reagents. On the other hand, few of them are electrolytes even when dissolved in ionizing solvents and, hence, the types

of reactions which are encountered are markedly different and the velocity of any changes is often found to be considerably lower.

In place of the exchange system of radicals as noted in inorganic reactions, we find in the organic field an analogous, but radically distinct, adherence to type. Thus, the atom of hydrogen which is connected to one of carbon can often be replaced by such non-ionic radicals as $-\text{NO}_2$, $-\text{Cl}$, $-\text{SO}_2\text{OH}$, $-\text{CN}$, etc., although this exchange may sometimes require an indirect series of transformations. As example, one might note that the hydrogen must first usually be displaced directly by chlorine, and then the product must be treated with an inorganic cyanide, in order to accomplish an introduction of the $-\text{CN}$ group in place of hydrogen.

Another respect in which the reactions of organic compounds are distinguished lies in the great tendency to form secondary products. Seldom does a change occur entirely according to a single type, but rather does one usually expect several to take place at the same time, each according to one of the known types or perhaps on a pattern which up to that time is absolutely unknown. The endeavor is, therefore, in any particular instance to regulate the various conditions in such a way as to obtain a maximum of the product desired and with little expectation ordinarily of being able to attain 100 per cent of the theoretically possible quantity. From an industrial standpoint, of course, this practically always results in obtaining a number of more or less valuable by-products.

In the matter of structure, also, the compounds of carbon are strikingly different. When we examine and critically analyze the probable make-up of atoms within the molecule of such substances as potassium dichromate, $\text{K}_2\text{Cr}_2\text{O}_7$, we picture the two chromium atoms as having no direct connection but as linked through an atom of oxygen; indeed, the properties of acids, bases and salts which, with their dehydrated products, constitute the substances known as inorganic compounds, are best represented by linking of atoms with oxygen as the connective agent, except in those few instances in which oxygen is not a constituent. At any rate, in practically all of these compounds, whether oxygen is present or not, we do not usually assume a linkage of two like atoms. For example, the structural formula of sodium sulfate, Na_2SO_4 , is not written in such a way as to connect one oxygen atom to another nor the two atoms of sodium to each other. In the case of carbon compounds, however, in order to account for numerous substances of similar or even identical formulas, it is a great convenience, if not an absolute necessity, to picture carbon atoms as bound directly to other carbon atoms. In fact, the whole organic system as used at present is based upon the assumption that the atom of carbon is more often than not linked to others of the same kind.

This view was instituted and is maintained largely because of a condition known as isomerism (like form), which is first met in the organic field. There are two compounds known with the formula C_6H_{10} and, although they are somewhat alike in most physical, chemical and physiological properties, there are enough differences to establish beyond doubt that they are distinct individuals. In other cases as many as fifteen or twenty separate compounds have been prepared, for each of which the same formula must be assigned after a careful analysis is made, and some of these may be entirely unlike the others in general character. The edifice of theoretical structure is so well built that one can often predict with

ertainty just how many compounds can be prepared which will have a given formula. For such a one as $C_{10}H_{22}$, for example, 75 compounds are known to be possible and there seems little doubt, based upon past experience and upon characteristics of those which are already known, that all of them could be made if it were necessary. On similar, theoretical grounds, it is known with great certainty that for some formulas there would be possible thousands and even millions of compounds. This condition, in which two or more different substances have the same formula, is known as isomerism and the compounds are said to be isomeric to, or isomers of, each other. In some instances the properties of isomers are very similar, while in others they may be very greatly different. Incidentally, there is undoubtedly isomerism in the inorganic realm, but it is not given much attention and is certainly not at present of great importance.

Finally, as another reason for separate study of organic chemistry, we might note one which is possibly erroneous but nevertheless sincerely conceived and mistakenly maintained. The statement is often made in textbooks that organic compounds are much more complex than inorganic ones and this is advanced as a powerful argument for presenting the chemistry of carbon at a different and later date than that of other elements. As a matter of fact, we know that such substances as silicates probably are much less simple than they are usually pictured, and it is perfectly possible that they can become as complicated as the corresponding compounds of carbon. Even in the case of substances which are ordinarily looked upon as very simple, we have very little means of knowing just how intricate is their molecular arrangement. Sodium nitrate may be $NaNO_x$, as usually given but it may just as well be $(NaNO_x)_y$, in which x is any whole number. We know for a fact that there are at least two oxides of mercury (ic), $(HgO)_x$ and $(HgO)_y$, although there is no means of fixing the exact value of either x or y . Indeed, one can give very critical attention to the character of inorganic compounds but a short time without coming to the conclusion that they may very readily be extremely complex in nature. The most which can be said with scientific exactness is that any possible high degree of intricacy in the molecules of inorganic compounds is of small actual importance at present, while the known complexity of some organic substances must be taken into account because of the practical significance of isomerism.

For the reasons given above and for others of minor nature, the study of carbon compounds is usually deferred. The student who begins such a course is presumed to have learned all of the fundamental principles and to have applied them to the reactions of other elements and to the compounds which can so be formed. Actually he can now apply the same principles to organic compounds and in somewhat the same way, but with increasing variation and modification as the substances become more complex.

Composition.—As a start in this instruction we would do best to note those elements that enter into substances containing carbon. A large majority, let us say about 85 per cent, contain only carbon, hydrogen, and oxygen, and these three thus represent the important nucleus of organic chemistry. The hydrocarbons, consisting of carbon and hydrogen solely and numbering many thousands, may be regarded as the parent substances, since all others may be derived from them by substituting for

bydrgoen. In addition to oxygen a great many of the other elements can be introduced into the molecules by known laboratory methods. Compounds containing nitrogen, sulfur, phosphorus, and the metals are common in nature, and those with the halogens are easily made. Although we also have combinations with others like arsenic and bismuth and some of these are important medicinals, yet in numbers they constitute but a small fraction of the whole. Perhaps it would be safe to say that practically all organic compounds are made up of carbon, hydrogen, oxygen, nitrogen, sulfur, phosphorus, and the halogens, if one excepts the salts with acids and bases, such as procaine borate and sodium acetate.

Analysis for Carbon and Hydrogen.—If a particular substance should be presented for investigation, it would be very convenient if one had some simple test by which it could be classified as organic or not. Fortunately we have the basis for such a test in that all compounds of carbon and hydrogen will burn in a sufficient supply of oxygen to carbon dioxide and water. Therefore, if the substance in question is mixed with an oxidizing agent such as copper oxide and heated to a moderate degree, it can be placed as a compound of carbon when carbon dioxide can be identified in the gaseous products. A still easier method is by simple heating, because practically all organic compounds will burn with a preliminary charring due to liberation of carbon. However, the result must sometimes be questioned, for a blackening may be due to certain metals, and absence of this effect will be noted in the case of substances which volatilize without decomposition. The usual procedure is to heat some of the material gradually, noting the appearance of any charring and whether any inorganic residue is left after the temperature is raised to redness. If the test indicates that the substance is entirely organic, this may be confirmed by the method first given or, as it is usually performed, by a quantitative estimation of carbon and hydrogen.

Having found that a given compound is organic and on the basis that most such have only three elements, the next step is to determine amounts. This is accomplished by mixing with a non-volatile oxidizing agent such as copper oxide and burning in a free supply of oxygen. The water and carbon dioxide that are produced are absorbed by sulfuric acid or calcium chloride and by potassium hydroxide or soda lime respectively, both contained in tubes that allow disconnection and weighing. In the absence of other elements, or with the quantity of such known, the percentages of carbon and of hydrogen are calculated and that of oxygen is given by subtraction from 100. The process is conducted in a special apparatus and is called a "combustion." Details and description of the method vary considerably and for these the student must be referred to one of the larger books noted in the appendix.

Nitrogen.—Many of the important compounds of pharmacy and medicine also contain nitrogen, and detection and estimation of this element are often necessary. Simple ignition frequently demonstrates the presence by producing an odor like that from burning hair or feathers. A more reliable method is to obtain ammonia by heating with lime or caustic alkalies. In both cases, however, a negative result is inconclusive, so that resort is usually made in the first place to treatment with metallic sodium, or better potassium. A small amount of the material is dropped into the highly heated metal, resulting in the formation of a metallic cyanide. At

e same time any halogens are converted to halide and sulfur is transformed to a sulfide. After decomposition of excess metal by means of alcohol and dilution with water, the cyanide is converted to ferrous double salt, and this gives a blue precipitate of ferric ferrocyanide upon addition of ferric salts in the presence of excess mineral acid. The equations for these reactions are probably already familiar to the student from his study of qualitative analysis and will be reviewed in a later chapter. Even if the blue color is not apparent because of its small amount, it may be made visible on white paper by filtration.

If the presence of nitrogen has been established, one may next determine its quantity. The older process of Dumas involves a modification of the combustion to convert the element into its free state and a measurement of the volume produced. While this method is still largely used because it is universally applicable, resort is being made more and more to processes that convert the nitrogen to ammonia. The most popular of these is some modification of the Kjeldahl method, which relies upon concentrated sulfuric acid as the transforming agent. In any event, the ammonia is finally liberated and converted into some derivative; in the Kjeldahl process the amount is estimated by reaction with acid of known volumetric strength. Detailed description and means of calculation for the various methods may be learned by consulting the reference books.

Other Elements.—Sulfur and the halogens are generally proved by examination of the liquid made after heating with sodium or potassium. The test for nitrogen. Portions of the solution are treated with sodium tetraphenylphosphide, which gives an evanescent violet color with sulfides, or with silver nitrate and excess of nitric acid, which give the usual qualitative reactions with halides and sulfides. Sulfur may also be detected by heating the substance with an oxidizing agent and testing the resulting mixture for sulfates. This also constitutes a means for determining the amount of sulfur, since it may thus be converted to barium sulfate which can be ignited and weighed. The halogens are estimated by weighing the silver compounds, often made directly by heating the substance with silver nitrate and nitric acid (Carius method). An unreliable but very convenient test for the presence of halogens is that of Beilstein which depends upon a green or blue color in the flame when metallic copper is heated with materials containing these elements.

Phosphorus is detected and determined by fusion with a nitrate or similar oxidizing agent. This results in the formation of phosphate that responds to the usual qualitative tests. Conversion to magnesium ammonium phosphate and ignition of this to the pyrophosphate provides a means for calculating percentage of this element in the sample.

Metallic constituents are identified in the ordinary manner, after burning off all organic matter by ignition. The quantity can also be calculated for each element from the results obtained in the usual reactions of analysis.

Formula.—Having learned which elements are present and in what amount, we may next need to find a formula. The identification of compounds that are already known can generally be accomplished by a study of physical properties and by conversion to derivatives, and these will be discussed briefly later. Presuming, however, that the substance is new, we naturally would like to establish its constitution. If we have made no error in our previous work, the formula can be derived by the methods

used in inorganic chemistry. We can calculate the relative number of atomic weights of each element by dividing the atomic weight into the total. The resulting figures can then be reduced to whole numbers through dividing or multiplying all of them by the same value. In order to bring this out more clearly, let us note an example.

A given compound (urea dihydrochloride) has been found to have the following composition: carbon 9.02, hydrogen 4.51, oxygen 12.03, chlorine 53.39, nitrogen 21.05 per cent. Dividing these figures by the respective atomic weights, we arrive at the formula



Since we must have a whole number of atoms (atomic weights), and none can be less than 1, we divide each by the smallest, 0.752, and get the empirical formula $\text{CH}_2\text{ON}_2\text{Cl}_2$.

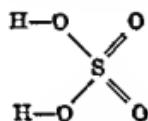
It is evident, however, that a formula with twice the number of each atom would just as well represent the percentage composition, as would also three times or any multiple. In other words, the formula of a compound with an analysis as given in our example must be $(\text{CH}_2\text{ON}_2\text{Cl}_2)_x$, where x is any whole number. If we could determine the value of x we could obtain a true "molecular formula."

Molecular Weight.—An experimental determination of molecular weight, even if not exact, would accomplish this purpose. It would be found near 133 if the value of x is one and near some multiple of this if the value of x is greater than one. In the case of gases, or of substances which can be converted into gases without decomposition, the molecular weight can be found by weighing a given volume, or by measuring the volume of a given weight, and calculating the number of grams in 22.38 liters under standard conditions of temperature and pressure. For those which cannot be so vaporized, the cryoscopic methods are available. These, as probably already familiar to the student, depend upon changes in the melting or boiling point of a particular solvent when known amounts of the substances are dissolved in this solvent; a gram-molecular weight in a given volume gives a constant value for the lowering of melting point or for the raising of boiling point, regardless of the substance dissolved, unless it is an electrolyte. For details of the processes the student is referred to the appropriate sources.

Very frequently it is much more useful to determine the molecular weight by making chemical derivatives. We can make a metal salt of acids and find out how much metal is contained in the product. Thus, acetic acid is found to have the formula $(\text{CH}_3\text{O})_x$, while the silver salt is $\text{AgC}_2\text{H}_4\text{O}_2$, thus showing that x is 2 and that the molecular formula is $\text{C}_2\text{H}_4\text{O}_2$. For bases we can make double salts with platinum chloride or a similar compound and again determine amount of the metal contained in the product. Thus, dimethylamine, which has been found to be $(\text{C}_2\text{H}_5\text{N})_x$, combines with platinum chloride in hydrochloric acid to give $(\text{C}_2\text{H}_5\text{N})_x\text{H}_2\text{PtCl}_6$, just as ammonia produces similarly $(\text{NH}_3)_x\text{H}_2\text{PtCl}_6$. Dimethylamine must, therefore, have the formula $\text{C}_2\text{H}_5\text{N}$. There are many varieties of methods used for other classes of compounds in order to determine the molecular formulas. A final illustration will be sufficient, however, to make the general system of procedure clear. The compound benzene, which has been found to have the formula $(\text{CH})_x$, reacts with chlorine to produce among others $(\text{C}_6\text{H}_5\text{Cl})_y$ and $(\text{C}_6\text{H}_5\text{Cl})_z$. Assuming

at one of these contains only 1 atom of chlorine, it is clear that the value of y must be 1 and z must be 2, or at least that $z = 2y$. The further study of other such derivatives leads to establishment of C_6H_6 as the molecular formula of benzene.

Structure.—We have already noted that a given molecular formula may present more than one compound, a fact which necessitates still more investigation to determine the constitution of our organic substance. In her words, we must find just how the atoms are linked together, the structural formula, since variations in arrangement are used to picture the differences in isomers and to represent the chemical properties. Until more information is available to the student, however, it is almost impossible to discuss methods for establishing the most representative structure. As this information is presented we will return to the subject repeatedly. In the meantime it should be emphasized that the molecular formula in organic chemistry is usually meaningless, because it may stand for many compounds, and that we must practically always note the structural or graphic formula or the more convenient rational or rationalized one. In the former we put each atom separately and indicate how it is connected; SO_4 , thus becomes



ince each hydroxyl radical is equal to the other and since the doubly bound oxygen atoms are equivalent, the rational or rationalized formula, O_2SO_2 , becomes more convenient.

Physical Properties.—The introduction to our subject would not be complete without referring to the common methods of ascertaining physical properties. A knowledge of these is essential for purpose of identification and to determine purity. The most important of these properties are melting or congealing point, boiling point, specific gravity, solubility, index of refraction, and optical rotation.

The melting point is of special significance in organic chemistry because large share of the compounds to be studied will melt before decomposition sets in and the temperature at which this occurs is a distinctive characteristic. For that reason, the determination of melting point is very frequently carried out in the laboratory and mentioned in the class-room. The student will quickly learn the established methods for performing the test and no discussion of these is necessary here. For preliminary reading along this line and for reliable directions in carrying it out he is referred to the Pharmacopœia.

It is well, however, to note one or two general facts about the melting point. The presence of impurities invariably lowers this, sometimes to a considerable degree, and this is true regardless of the melting point possessed by the impurity. Investigation of a new substance, therefore, involves treatment designed to purify until any further continuation no longer raises the melting point. Again, any question of identity of two substances which melt at nearly the same temperature can be solved by mixing the two and noting if the point has been lowered. If any considerable quantity of impurity is present the melting point becomes very

indefinite and irregular, so that sharpness of melting can be used as a criterion of purity. The relation of structure to this physical property and the comparative values in isomeric compounds will be considered in later pages.

The boiling point is just as much a specific characteristic and test for purity in those compounds which can be distilled without decomposition. For details of methods consult the larger texts or the *Pharmacopœia*.

The value for mixtures depends on the nature of the components. An alcohol-water solution begins to boil at about 78° and the distillate will at first contain mostly alcohol. The amount of water increases until the last portion comes over at about 100° . On the other hand, a mixture of turpentine oil (155° to 156°) and considerable water (100°) will distil almost entirely at about 92° until all of the oil and most of the water are in the receiver. This distillation with water (steam) can be utilized to separate such an insoluble substance from non-volatile impurities.

When the substance decomposes if heated to the boiling point, it can often be distilled at a lower temperature if the pressure is reduced. This distillation under reduced pressure is frequently employed in the laboratory as the only available means of purification. Near the boiling point there is a decrease in this constant of about one degree for every 27 mm.

In use of a thermometer, as in melting and boiling points, a correction must be made if the whole mercury column is not in the heated system, unless the instrument has been graduated and is marked as partial immersion. The number of degrees to be added is $N(T-t) 0.000154$, where N is the number of scale divisions not in the measured temperature T , but at a lower point t , as measured by another thermometer.

The solubility is also of practical importance, chiefly for separation and purification. In general, organic substances are not very soluble in water, even less so as the molecular weight becomes higher, but dissolve in alcohol and other organic liquids. If oxygen is present in the molecule, especially as hydroxyl, the solubility in water is usually higher.

In examination of a new substance for solubility, it is usually not necessary to determine this quantitatively. A rough approximation for each solvent will suffice. For accurate estimation a measured amount of saturated solution may be evaporated if the substance is not volatile, but for liquids and volatile solids a weighed quantity of the material is treated with solvent until the first mixture becomes homogeneous. In case only small amounts are available and the solvent apparently brings about no solution, evaporation of a few drops of the supernatant liquid will demonstrate whether any at all has occurred.

Knowledge of approximate solubility is utilized practically in two directions. The components of a mixture may often be separated by extraction with the appropriate solvent or combination of solvents. This is frequently employed to isolate vegetable substances, to prepare tinctures and other galenicals, to separate the various products of a manufacturing process, to extract poisons for identification, and for many other purposes. It is also of great value to the organic chemist as a means for recrystallizing solid compounds to remove impurities. The ideal solvent for this purpose would easily take up the compound at higher temperature but redeposit it upon cooling; the chance that the impurities would behave in the same way is small. In the absence of such a solvent, one could dissolve in some liquid

and precipitate by the addition of another which is miscible with the first but in which the compound will not dissolve. Such methods of recrystallization are indispensable aids to practical laboratory procedure but cannot be elaborated further in this volume.

The index of refraction of transparent or translucent liquids is often an essential criterion of purity and, as we shall see, can be used to decide questions of structure. The constant, designated by the symbol n , is expressed mathematically as $\frac{\sin i}{\sin r}$ where i is the angle of incidence and r is the angle of refraction. For an excellent discussion of the principles and technique consult the U.S.P. page 608. The values obtained for common liquids are from 1.3 to 1.7; thus, peppermint oil gives 1.4820 to 1.4900 at 20° . For pure compounds we eliminate the influence of temperature and density by calculating the specific refraction as $\frac{n-1}{d}$ (Gladstone)

or $\frac{n^2-1}{n^2+2} \cdot \frac{1}{d}$ (Lorenz and Lorentz), where d is the specific gravity at the temperature at which n was measured. Multiplying the specific refraction by the molecular weight gives the molecular refraction. Since this value can also be calculated from a knowledge of structural formula, conversely we can often utilize it to settle questions of structure.

Optical rotation, or rotation of the plane in polarized light, is a property possessed by many organic compounds. Those which turn this plane to the right are called dextro-, to the left levo- or levo-, rotatory. The student is advised to consult the U.S.P. pages 601-603 or some larger text for details of theory and methods. The subject is very important, but any further discussion will be postponed until we bring up a substance which exhibits this property.

Other physical constants, such as conductivity, viscosity, and surface tension have probably been studied at a previous time. They will be referred to occasionally in later pages and may profitably be reviewed by the student at this point.

Definition of Organic Chemistry.—Finally, in this introduction we must refer in some greater detail to a definition of our subject. Every compound coming within its scope may be looked upon as derived originally from one containing only hydrogen and carbon by substitution of the former by means of some other element or radical. We logically start any study, therefore, with learning about these compounds of carbon and hydrogen, the hydrocarbons, and then proceed to the classes, one at a time, in which replacement has taken place. A common definition of organic chemistry is "a study of the compounds of carbon." For purposes of study and teaching, however, it seems much better to look upon it as a course concerning "the hydrocarbons and their substitution products." The next chapter will begin a discussion of these hydrocarbons.

REVIEW QUESTIONS

1. How is each of the common elements detected in organic compounds?
2. How is each determined quantitatively?
3. Given the --- . . .
 - (a) Carl
 - (b) Cart
 - (c) Cart

INTRODUCTION

Use these atomic weights: carbon 12, hydrogen 1, oxygen 16, chlorine 35.5, nitrogen 14.

4. What else is necessary to determine correct molecular formula? How is it used?
5. Explain the differences between molecular, structural, and rational formulas, using H_2SO_4 as illustration.
6. How can one use the melting point to determine identity?
7. What is the correction for emergent stem in determination of melting or boiling point?
8. How does the boiling point change with alterations of pressure?
9. Explain the proper way to recrystallize a given compound.
10. Define index of refraction, organic chemistry, optical rotation.

CHAPTER II

THE METHANE SERIES

IN the study of carbon during a beginning course, you have learned that there are two oxides, CO_2 and CO , in one of which the valence is 4 and in the other 2. You also found that the latter oxide has ability to add things and become saturated, thereby increasing the valence of carbon to 4. Position in the periodic system would tend to confirm these two values as the possible valences for this element and, from careful study and analysis, we conclude that 4 is the logical and stable valence. As a matter of fact, the whole superstructure of organic chemistry has been formulated on the assumption that the carbon always has such a valence. Carbon monoxide represents a probable exception, undoubted if we assign 2 to oxygen, and there are a few other compounds in which carbon may have a lower value than 4, but in all such the stability is so low that we assume the remaining, unconnecting bonds can easily be utilized. Because all later considerations fall nicely into prescribed niches and facilitate study and research, we start with the fundamental basis that carbon has a valence of 4 at all times.

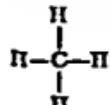
Three other basic tenets are required and recognized. In the first place, we must assume that carbon atoms can be united to carbon by one or more linkages, a condition which we have already seen is unusual in inorganic chemistry for other elements. Especially is this conception necessary in the explanation of certain isomers. Secondly, no free valences are recognized and, finally, all four bonds from an atom of carbon are equal in value. If we liken the carbon atom to a tetrahedron, the four valences must logically be exerted in the direction of the vertices, whether connected to another atom of carbon or to a different element.



We start then with these four fundamental assumptions as the groundwork for theoretical organic chemistry:

- (a) The valence of carbon is four.
- (b) The atoms of carbon may be connected to each other.
- (c) There are no free valences.
- (d) All four valences of a carbon atom are equal.

Methane.—The simplest of hydrocarbons would have the graphic or structural formula



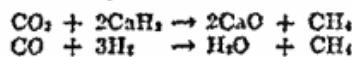
or, since the four valences are equal and also the four atoms of hydrogen, the rational formula CH_4 . This compound is methane or marsh gas which

is present in the gases arising from swamps or from rotting vegetable matter. It is present in natural gas up to 95 per cent, in coal gas 30 to 40 per cent, and in water gas 6 to 12 per cent. It is frequently found in mines where, mixed with air, it is called fire-damp.

Methane is a gas with a slightly onion-like odor, a boiling point of about -164° , a melting point of about -184° , and a critical temperature of -82° at 55 atmospheres. It is not soluble in water but will dissolve readily in alcohol or ether.

Many methods of preparation are known although most of them have little practical significance. Those which represent means for making this important compound are especially interesting. One method in the presence of nickel; the chief product is acetylene, C_2H_2 .

2. From the monoxide or dioxide of carbon, either of which can be made by union of carbon and oxygen, by passing them over hot calcium hydride; exposing a mixture with hydrogen to an electric spark; or passing such a mixture over hot, freshly reduced nickel.



3. From a mixture of carbon disulfide and hydrogen sulfide over red-hot copper. Water can replace the hydrogen sulfide.



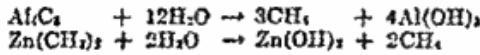
4. By the action of nascent hydrogen on carbon tetrachloride, chloroform, or other halogen substitution product.



The hydrogen may here be generated in a variety of ways but usually by the zinc-copper (Gladstone) couple or by sodium amalgam and water.

Some of the methods are analytical or "ahau" and these are often more practical in the laboratory.

5. The hydrolysis of some metallic carbides, of metallic methides, or of the Grignard reagent. These will be further discussed in Chapter XX.



6. Heating of acetates with bases like soda-lime. This common laboratory method will be described more extensively in Chapter XII.



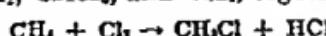
7. By the anaerobic fermentation of cellulose or other carbohydrates, a method which can be used commercially and has been known for nearly fifty years.

8. By degradation of other hydrocarbons at high temperature. Methane is obtained as one product in cracking petroleum (Chapter III) and in the destructive distillation of wood, peat, fats, carbohydrates, and many other natural materials.

Commercially methane is manufactured as in 2 from water gas, essentially a mixture of carbon monoxide and hydrogen, by passing it over nickel at 400° .

Methane burns with a yellowish flame and forms explosive mixtures with air or oxygen. It explodes with fluorine at any temperature down to -185° and also with chlorine in the sunlight to form carbon and hydro-

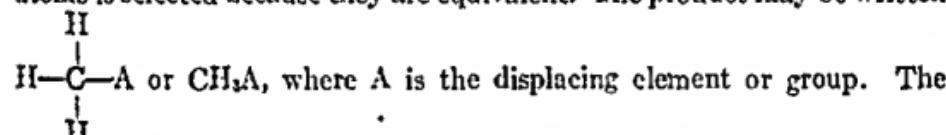
gen chloride. In diffused light chlorine or bromine forms substitution products: CH_3X , CH_2X_2 , CHX_3 , and CX_4 , together with hydrohalogen.



At elevated temperatures or under the influence of an electric spark, methane is decomposed to carbon and hydrogen or to other hydrocarbons. Under the same conditions in the presence of various reagents it is converted to other carbon compounds. Thus ammonia in the presence of aluminum oxide at about 1000° gives hydrogen cyanide, HCN. With steam over nickel at about 900° the chief products are carbon dioxide and hydrogen. This is said to be the most economical source for the latter to be used for the hydrogenation of coal (Chapter III).

At ordinary temperatures, however, and without the influence of extraordinary sources of energy, methane is quite stable to common agents except the halogens; iodine usually gives no reaction unless special provision is made.

A hydrogen atom of methane can be replaced or substituted by means of other elements or radicals, even though this cannot be brought about directly. Naturally it makes no difference which of the four hydrogen atoms is selected because they are equivalent. The product may be written



monovalent radical CH_2- , which is thus obtained from methane by subtracting one atom of hydrogen, is called methyl. We thus have methyl chloride, CH_2-Cl , and methyl oxide (CH_2)₂O.

Other Members.—Also known are many hydrocarbons which are similar to methane in physical and chemical properties. When arranged in order of molecular weight, the formulas are found to increase by two hydrogen atoms for each additional carbon atom. Any such series of carbon compounds, and there are many, in which each member differs from the preceding and succeeding ones by CH_2 , is termed an homologous series and the individual members are called homologues. The particular group containing methane is called the marsh gas or methane series and also, for reasons which will later be more apparent, the paraffin or saturated series. Because there is a regular progression by CH_2 , we can write a general formula for the whole class, $\text{C}_n\text{H}_{2n+2}$, in which n is any whole number. The names, formulas and some physical properties of the first twelve members are shown in the following table:

Name	Molecular formula	Boiling point	Melting point	Specific gravity
Methane	CH_4	-161	-164	
Ethane	C_2H_6	-84	-172	
Propane	C_3H_8	-45	-190	
Butane	C_4H_{10}	+1	-135	
Pentane	C_5H_{12}	+36	-132	
Hexane	C_6H_{14}	+71	-94	
Heptane	C_7H_{16}	+94	-90	0.7006
Octane	C_8H_{18}	+125	-57	0.7115
Nonane	C_9H_{20}	+150	-51	0.7330
Decane	$\text{C}_{10}\text{H}_{22}$	+173	-32	0.7456
Undecane	$\text{C}_{11}\text{H}_{24}$	+194	-26	0.7448
Dodecane	$\text{C}_{12}\text{H}_{26}$	+214	-12	0.7730

The lower ones are seen to be gases and the higher ones liquids, with a fairly constant increase in boiling point with rise in molecular weight. Those with more than 12 carbon atoms follow the same general rule, those with 17 or higher being solids above 20°. The figures given are for normal compounds, a statement which can only be appreciated later. It will be noted that the names from pentane on are made with Greek prefixes to designate the number of carbon atoms.

Ethane, C_2H_6 , must have the structural formula, $\begin{array}{c} H & H \\ | & | \\ H-C-C-H \\ | & | \\ H & H \end{array}$ or

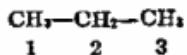
CH_3-CH_3 , since no other is possible if we give carbon a valence of four and hydrogen one. One may look upon this as derived from methane by substituting the methyl radical for one atom of hydrogen and it may be, and is, called from this point of view methylmethane. The added CH_2 for making the homologue, ethane, from methane is formulated by such replacement.

Propane is obtained theoretically from ethane by a similar substitution. The three hydrogen atoms of either methyl group of ethane are equivalent, and it is also apparent that it makes no difference which one of the six atoms is selected. There is, therefore, but one formula possible,

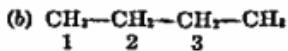
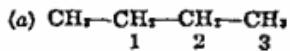
$\begin{array}{c} H & H & H \\ | & | & | \\ H-C-C-C-H \text{ or rationally } CH_3-CH_2-CH_3. \text{ It may be designated} \\ | & | & | \\ H & H & H \end{array}$

as dimethylmethane or, if the removal of hydrogen from ethane gives the ethyl radical, CH_3-CH_2- , also ethylmethane.

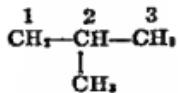
Butanes.—Proceeding in this manner to a derivation of butane from propane, we find that replacement of hydrogen by methyl gives two different compounds. In propane



all of the six hydrogens at 1 and 3 are equivalent, and substitution gives the compounds,



which are identical. However, if those numbered 2 are selected, we get



which is different from (a) and (b) above. When this compound was first prepared, because it is isomeric with butane (a), it was called isobutane meaning "like" butane. This particular form of isomerism, in which similar compounds have the same empirical formula but differ in position of branches, is called chain isomerism. Physical properties of the two compounds show differences, the boiling point and melting point of butane being +1° and -135°, those of isobutane being -10° and -145° respectively.

Later, as the existence of isomerism became increasingly important, names were given to these two compounds similar to those which have already been given for ethane and propane. Butane thus became ethylmethylmethane, while isobutane became trimethylmethane. In this method of naming as a derivative of methane, one can often select any one of several carbon atoms as the reference one, but the rule is to choose one with the least hydrogen and name the modifying radicals in alphabetical order. Thus, butane is ethylmethylmethane and not propylmethane or methylpropylmethane.

We have derived the three monovalent radicals, methyl, ethyl, and propyl, by subtracting one atom of hydrogen from the hydrocarbon. In the case of methane it made no difference which of the four was thus removed to give the radical, CH_3- . The same condition was found with ethane because all six hydrogens are equivalent and the radical can have but one formula, CH_3-CH_2- . From propane, however, we can get two such groups: $\text{CH}_3-\text{CH}_2-\text{CH}_2-$ which is called normal-propyl; and $\text{CH}_3-\text{CH}-\text{CH}_3$ which we term isopropyl. Such monovalent radicals,

made by removing one atom of hydrogen from a hydrocarbon, are called collectively "alkyl radicals" and may be designated by the general symbol R. Those from the methane series have the general formula $\text{C}_n\text{H}_{2n+1}-$.

Any hydrocarbon in the series may be derived from one with a smaller molecular weight by substituting an alkyl radical for hydrogen, as we have already done in getting the first four. In proceeding from a given hydrocarbon to the next higher, we replace one hydrogen by a methyl group. If all hydrogens in the compound are equivalent, then but one product is possible, but first in propane we find two different kinds, and this leads to two butanes. In general the compounds in straight chains without branches are called normal, abbreviated n-.

Summarizing to this point in the series we have

CH_4		methane
C_2H_6	CH_3-CH_2-	ethane or methylmethane
C_3H_8	$\text{CH}_3-\text{CH}_2-\text{CH}_3$	propane or dimethylmethane
C_4H_{10}	$\text{CH}_3-\text{CH}_2-\text{CH}_2-\text{CH}_3$	n-butane or ethylmethylmethane
	$\text{CH}_3-\text{CH}-\text{CH}_3$	isobutane or trimethylmethane
	\downarrow CH_3	

The butyl radicals, derived as before by abstracting one atom of hydrogen, are four in number. Of the ten hydrogens in n-butane, six are obviously alike but different from the other four which are also alike. Therefore, two radicals can be derived from it.

- (1) $\text{CH}_3-\text{CH}_2-\text{CH}_2-\text{CH}_3$ n-butyl
- (2) $\text{CH}_3-\text{CH}_2-\text{CH}-\text{CH}_3$ secondary (sec)-butyl

From isobutane by similar reasoning we also get two.

- (3) $\text{CH}_3-\text{CH}-\text{CH}_2-$ isobutyl
-
- (4) $\text{CH}_3-\text{C}-\text{CH}_3$ tertiary (tert)-butyl

A carbon atom linked to only one other carbon is called primary, one linked to two others secondary, and one bound to three others is called tertiary. The names for sec-butyl and tert-butyl radicals follow. On the same system isopropyl should perhaps have been called sec-propyl.

Pentanes.—In order to arrive at the formulas for the possible pentanes we would substitute a methyl radical for one hydrogen in butane. This is obviously equivalent to combining methyl with each of the butyl radicals. Of the four compounds thus formulated two are found to be identical, those from sec-butyl and from isobutyl.

(1) $\text{CH}_3\text{---CH}_2\text{---CH}_2\text{---CH}_2\text{---CH}_3$	n-pentane, diethylmethane, or methyl-n-propylmethane
(2) $\text{CH}_3\text{---CH}_2\text{---}\underset{\text{CH}_3}{\text{CH}}\text{---CH}_2\text{---CH}_3$	isopentane or ethyldimethylmethane
$\text{CH}_3\text{---CH}_2\text{---CH}_2\text{---}\underset{\text{CH}_3}{\text{CH}}_2\text{---CH}_3$	identical with (2)
(3) $\text{CH}_3\text{---}\underset{\text{CH}_3}{\text{C}}\text{---CH}_3$	neopentane or tetramethylmethane

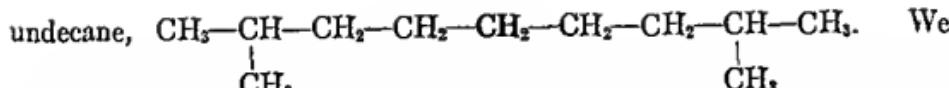
The substituting methyl group has been underlined in each case. There are, therefore, three known pentanes.

Hexanes.—We can derive in the same way the five possible hexanes.

(1) $\text{CH}_3\text{---CH}_2\text{---CH}_2\text{---CH}_2\text{---CH}_2\text{---CH}_3$	n-hexane, ethyl-n-propylmethane, or n-butydimethylmethane
(2) $\text{CH}_3\text{---CH}_2\text{---CH}_2\text{---}\underset{\text{CH}_3}{\text{CH}}\text{---CH}_2\text{---CH}_3$	iso-hexane or dimethyl-n-propylmethane
(3) $\text{CH}_3\text{---CH}_2\text{---}\underset{\text{CH}_3}{\text{CH}}\text{---CH}_2\text{---CH}_3$	diethylmethylmethane
(4) $\text{CH}_3\text{---}\underset{\text{CH}_3}{\text{CH}}\text{---CH}_2\text{---CH}_3$	isopropyldimethylmethane
(5) $\text{CH}_3\text{---}\underset{\text{CH}_3}{\text{C}}\text{---CH}_2\text{---CH}_3$	ethyltrimethylmethane

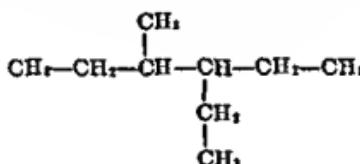
In a similar way we could obtain formulas for the 9 heptanes, for the 18 octanes, for the 35 nonanes, for the 75 decanes, for the 159 undecanes, and for the 355 dodecanes.

It is probably already apparent that a more reliable system of nomenclature must be devised. We might name one of the hexanes normal, a second one iso, and then devise other prefixes to designate the other three. For each one of numerous isomers of higher formulas we would need a new prefix, and the system becomes impracticable. The method which considers the substances as derived from methane answers satisfactorily but little further. Just as soon as the radicals have more than three atoms of carbon, a system of prefixes must again be adopted. Consider, for example, the



might call this di(?)pentylmethane, (?)bexylisobutylmethane, (?)beptylisopropylmethane, or dimethyl-(?)octylmethane, but in each case we would need some prefix in place of the interrogation mark to indicate which of the numerous radicals is involved. As the complexity grows the difficulties become more numerous, and the need for an explicable and efficient system of naming is increasingly evident.

Such a system was devised in 1892, when an international congress at Geneva issued a set of rules for denoting organic compounds, not only hydrocarbons but others as well. Instead of methane as the underlying substance, the longest chain is selected, and the side-chains are designated as alkyl derivatives, position being indicated by number. The formula last given above becomes 2,8-dimethylnonane, because it can be derived from nonane by replacing hydrogens at the second and eighth positions by methyl radicals. The name 3-ethyl-4-methylhexane stands for a compound of the formula



In setting down the name for a given formula, the first thing to do is to mark the longest chain and number the carbons in this chain. Conversely, to write the formula for a given name, put down the indicated number of carbon atoms in a straight chain, attach the groups called for at the proper place, and complete the formula with hydrogen. The so-called Geneva names will be used frequently, and the student will do well to practice at constructing names from formulas and vice versa. At the same time, the older systems of nomenclature are used for simple compounds and should be well learned.

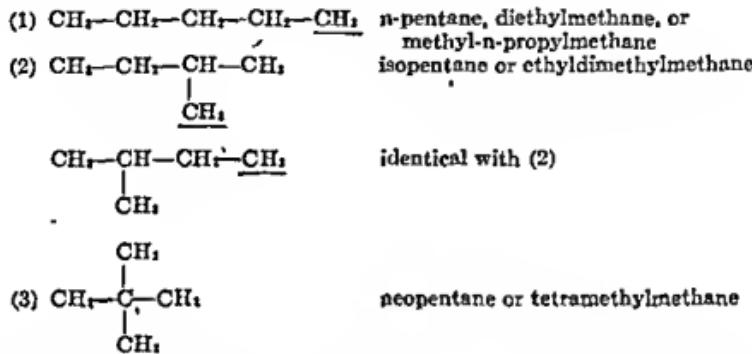
It is interesting to note the possibilities when the number of carbon atoms becomes higher than twelve. Since there are 159 undecanes and 355 dodecanes, one could readily come to the apparent conclusion that the number of isomers would soon become very large. For a given value of n in the general formula one could find the total number of probable compounds by a process of writing out each possible formula, an immense labor if n is very large. We might also devise a mathematical formula for calculating the number of possibilities and by such a formula the following figures have been obtained as approximate ones for given values of n :

n	Number of isomers calculated
13	about 800
20	about 115,000 or 10^5
30	about 100,000,000 or 10^8
40	about 10^{11}
50	about 10^{14}
60	about 10^{17}

Considering the value of n in some of the compounds which have been made, the total number of possible compounds is truly stupendous. While

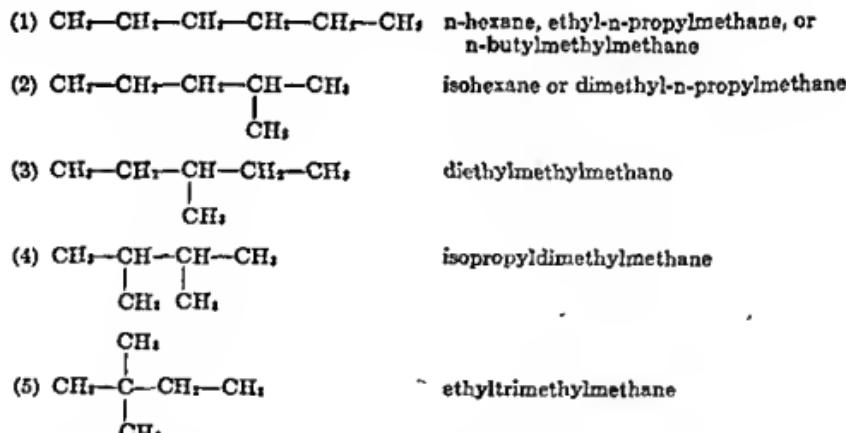
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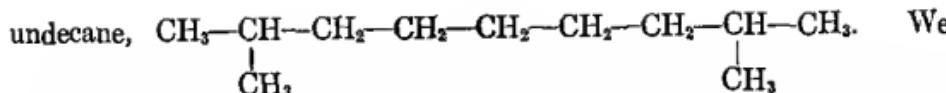
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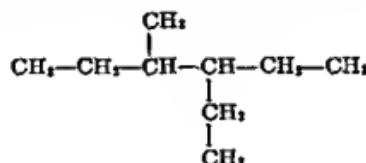
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REVIEW QUESTIONS

1. Upon what four assumptions is the structure of organic compounds based?
2. State three methods by which methane is made and write equations.
3. Name the first twelve normal hydrocarbons of the methane series and write their molecular and rational formulas.
4. Give three other names to the methane series.
5. Define the following terms: homologue, homologous series, alkyl radical, primary, secondary, tertiary, dextro, levo, racemic, asymmetric carbon atom, optical isomerism, stereo-isomerism.
6. For what does each of the following symbols stand: n, R, Me, IPr, Bu, Et, Pr, d-, l-, dl-, sec.
7. Write down the formulas of all possible butanes, pentanes, hexanes, and heptanes and name each as a derivative of methane and by the Geneva system.
8. What is the general formula of a member of the methane series and of an alkyl radical?

CHAPTER III

THE METHANE SERIES (*Continued*)

Occurrence.—Members of the series occur in petroleum and other natural materials. While some varieties of crude oil consist very largely of paraffins, most of them are conglomerate mixtures of hydrocarbons belonging to this and other series, and some of them have practically none of the saturated group at all. In addition, many of the varieties contain compounds of oxygen, nitrogen, and sulfur. Natural gas furnishes some of the lower members, especially methane which may constitute as much as 95 per cent. Ozokerite or ceresine, which is found in Galicia, Russia, and a few other places, is a mixture of solid hydrocarbons with a melting point of 60° to 80°.

By the distillation of other natural materials a product is obtained that resembles crude oil and contains some of the saturated series. In Scotland much shale is so distilled to give about 20 gallons of oil and 40 pounds of ammonium sulfate per ton. Most coals yield ordinary coal-tar, but varieties called brown, cannel, boghead, and pit often give oils that contain more or less of the paraffins. Similar heating of wood, fats, peat, and other materials furnishes oily distillates from which at least some hydrocarbons of this series may be separated. Substances very like crude petroleum are also now obtained by combined distillation and hydrogenation of coal dust in the Bergius process. In Europe, and especially Germany, this process has become important for the production of motor fuel. It is further interesting to note that, by the steam distillation of oleoresins from *Pinus jeffreyi* and *Pinus sabiniana*, there can be obtained oils which are mostly n-heptane. Undoubtedly this is the only instance where individual paraffins can be obtained unmixed with others of the series. Finally, it should be mentioned that mixtures of saturated hydrocarbons frequently constitute the wax-like material from flowers, leaves and other parts of plants.

None of these substances, however, is an economical source for individual pure compounds. It might seem feasible to separate the ingredients by a process of distillation, because the boiling points for members of the series differ somewhat as molecular weight increases or branching occurs. Practically this can be done only to a limited extent, so that the commercial products are partly purified mixtures of hydrocarbons which boil within a comparatively narrow range.

Petroleum Technology.—Crude oil is the chief source of the compounds belonging to the methane series, although no single one of its members is obtained in the pure state. As has been mentioned, hydrogenation of coal and the distillation of other materials produces similar oils which could be worked up in the same way to commercial mixtures of more or less value.

Petroleum is found in almost every country in the world and in many sections of the United States. No one can say definitely just how it has been formed in the earth, although many maintain that it must have been

many western oils, is used in road-building, paints, insulation, waterproofing, and for other purposes.

Natural Gas.—Frequently accompanying crude oil in a tapped well is a natural gas, and sometimes this is the sole output of a well. This gas contains methane and other lower hydrocarbons of the saturated series, usually mixed with impurities such as nitrogen and carbon dioxide, also often with higher paraffins that can be removed by cooling and compression (casinghead gasoline). A composite analysis shows 15 to 97 per cent of methane, 0.9 to 21 per cent of other hydrocarbons, up to 15 per cent of carbon dioxide, 1 to 82 per cent of nitrogen, and about 1 per cent of other ingredients. Included in the last in certain western districts is a notable amount of helium, which is being recovered by private interests under strict control of the Federal government. In many localities the natural gas is utilized as a cheap fuel and it is even piped to far distant communities; in fact, a large share of the United States is now being supplied with this useful mixture.

Physical Properties.—The paraffin hydrocarbons are almost if not entirely insoluble in water. Alcohol dissolves the gaseous ones to some extent and the lower liquids easily, while the higher compounds dissolve with increasing difficulty as the molecular weight becomes larger. They are generally soluble in chloroform, ether, benzene, carbon disulfide, and many fixed and volatile oils. Some of the other physical constants have already been noted in Chapter II.

Preparation.—When pure compounds of the methane series must be obtained, it is necessary to utilize the reactions of their substitution products. Since an understanding of the methods used must involve discussion of the derivatives that are needed, we must postpone details until we come to a consideration of these compounds and their properties. The five common methods of producing the paraffins are here merely listed, with notations as to where they will be considered in greater detail.

1. Action of heat on a mixture of organic salt with sodium hydroxide or soda lime. (Chapter XII.) It will be remembered that methane is produced if we use sodium acetate as the salt.

2. Reduction of halogen derivatives, unsaturated hydrocarbons, aldehydes, ketones, or acid derivatives by means of nascent hydrogen or of hydrogen and a catalytic agent. (Chapters IV, V, VII, IX, X, XII.)

3. Through the Grignard reaction using an alkyl halide and magnesium in ether solution with subsequent hydrolysis. (Chapters IV and XX.)

4. Heating one or more alkyl halides with a metal like sodium or zinc (Wurtz reaction). (Chapters IV and XX.)

5. Electrolysis of salts of dibasic acids. (Chapter XV.)

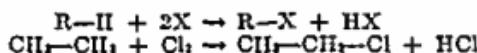
It must again be emphasized that in all cases there are other products than the substance desired and that the latter must be purified. Recently it has been found that higher paraffins can be made by the reaction of carbon monoxide and hydrogen in the presence of certain catalytic agents such as ruthenium. In this way materials have been obtained with melting points up to 132° and molecular weights as high as 7000.

Reactions.—The chemical properties at room temperatures are relatively few. Indeed, the inactivity toward most reagents led to the general name

paraffins for this series, from *parvum affinis*, meaning "little affinity." Sulfuric acid or sodium hydroxide has practically no action at any temperature, and no effect can be obtained in the cold with fuming nitric acid, chromic acid, or potassium permanganate. The compounds are inflammable, burning with a sooty flame except the lower gases, but a definite kindling temperature is necessary.

Halogenation.—The only agents which will attack the paraffins at ordinary temperatures are the halogens. Fluorine, as you remember, combines so actively with methane as to cause explosions, even at very low temperatures. The violence of union is moderated with the higher hydrocarbons but is very rapid with any of them. Chlorine attacks all of them slowly, more rapidly in sunlight or in the presence of so-called carriers. The most energetic of these carriers is iodine which undoubtedly forms chlorides such as ICl_5 as intermediates. Iron or its salts and compounds of tin, antimony, and aluminum are also employed as halogen carriers. Bromine is much less active but does brominate the paraffin slowly if carriers are used especially at a higher temperature. Iodine does not give any effect at all unless something is added to remove the strongly reducing hydrogen iodide which is formed. The latter reverses the halogenation unless it is withdrawn by action of mercuric oxide, iodic acid, or a similar compound.

The process of halogenation (chlorination or bromination) is one of substitution, and the products are called halides or halogen derivatives.



Hydrohalogen is set free in all cases, as can be easily demonstrated; identification of its presence is assumed as positive evidence that substitution has taken place.

In all of the hydrocarbons there is more than one atom of hydrogen that can be affected. With excess of the halogen each of these may be substituted one at a time, so that a mixture of halides is the final result. By altering the conditions, it is often possible to control the reaction in such a way as to obtain replacement of a given number of hydrogen atoms, but in all cases the yield of desired compounds is always low. Usually there results a complex mixture that only becomes of value if it can be separated into its components. From ethane, for example, we might obtain any one of nine possible compounds or mixtures of several. Halogenation is, therefore, a poor method of preparing the halogen derivatives. When the required product is a monohalide and there is but one probable point of attack, chlorination or bromination may be used efficiently. In general also the hydrogen of a tertiary carbon atom is more easily affected than that of a secondary or primary one.

At higher temperatures the paraffins become quite reactive to certain reagents. Oxidation will take place readily in air or oxygen, or with agents which furnish nascent oxygen. The products are usually carbon and water or carbon dioxide and water, depending on amount and activity of the reagent; hence, the oxidation of compounds belonging to this series is of no importance in producing substitution products. Fuming sulfuric acid can be made to attack the paraffins at elevated temperature, usually as

oxidizing agent but in a few cases to give condensation, especially with tertiary hydrogen.



The process is called sulfonation and the products are sulfonic acids. Nitric acid, which generally and mostly oxidizes, can act in a similar way by nitration to yield nitro compounds.



In the laboratory, it is at present not easy or not important to produce nitro or sulfonic compounds of the paraffins, but the industrial manufacture of such substances is being carried out, and several of them are available commercially.

The most significant action at high temperature is decomposition to form compounds with lower molecular weight, a condition which makes possible the process of petroleum cracking. The product in each case is a complex mixture, and as yet one cannot predict what will result from an individual compound. Ethane forms a compound called ethylene and some methane, among others, but our knowledge is too incomplete to say that it does so according to the exact equation: $2\text{C}_2\text{H}_6 \rightarrow 2\text{CH}_4 + \text{C}_2\text{H}_4$. All we can say definitely is that a mixture of paraffins of lower molecular weight and other unsaturated hydrocarbons will be obtained.

This decomposition by heat, or pyrolysis, is largely used for the higher compounds in order to get gasoline from them. It is said that by combining the process with hydrogenation practically all of the crude oil can be converted to motor fuel. This hydrogenation may be illustrated by the equation for the product from ethylene: $C_2H_4 + H_2 \rightarrow C_2H_6$.

REVIEW QUESTIONS

CHAPTER IV

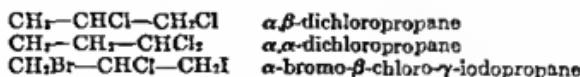
HALOGEN DERIVATIVES

IN the last chapter we noted that halogenation of the paraffins leads to substitution products. We learned further that this reaction represents the only property of hydrogen in a hydrocarbon radical that could be used in the laboratory to convert these compounds to useful derivatives. Finally, we found that the products are generally mixtures and came to the conclusion that the paraffins are not good starting points to prepare the substituted molecules, although this can be done industrially through the pyrolytic methods. The halides, however, can be obtained for laboratory use by other means and prove exceptionally useful in preparing many compounds that are of value.

Each hydrocarbon of the series can furnish from four to hundreds of different halides, so that the total number becomes immensely larger than that of the paraffins. For example, there is only 1 ethane but 9 compounds from it by substituting each of the halogens, a total of 36, and with more than one replacement we can have many mixed halogens to raise the total to well over a hundred. With propane and the higher homologues the number of possible derivatives becomes almost infinite. Fortunately a few only of these possibilities are of practical importance.

Nomenclature.—The usual methods follow the general principles already expressed. Those substances containing but one atom of halogen are designated by the radicals to which the atom is linked, but this can be done only up to the point beyond which it is impracticable to give such radicals a name. Thus, we have ethyl bromide, n-propyl iodide, secondary-butyl chloride, etc. When the alkyl becomes too branched for simple naming, the Geneva system is preferable using the prefixes chloro-, bromo-, iodo-, and fluoro- for the substituent. This system is also best for poly-halogen compounds; n-propyl bromide would be 1-bromopropane and $\text{CH}_3\text{---CHCl---CH}(\text{CH}_3)\text{---CHCl}_2$ would be 2-methyl-1,1,3-trichlorobutane. The final o of these prefixes is sometimes omitted.

Still another method is used when the compound contains several halogen atoms. This employs Greek letters to denote the carbon atoms instead of Arabic numerals. Three examples should suffice to make the names clear.



This system is sometimes applied to other polysubstituted compounds besides halides.

For a few of the simple derivatives we have still one more method of designation. For products from methane we have methyl halide, CH_3X , methylene halide, CH_2X_2 , and methenyl halide, CHX_3 . When two substituents have the same valence there are two possible isomeric compounds: $\text{H}_2\text{C=CHX}_2$ and $\text{CH}_2=\text{CHX}_2$. These are called ethylene halide and vinyl halide. We thus have special names for the divalent CH_2X_2 , and $\text{CH}_2=\text{CHX}_2$, and for the trivalent CHX_3 . Sometimes such designations are extended to the higher homologues,

giving for the group R—CH= alkylidene and for R—CH—CH₂= alkylene. Propylene chloride would in this way be CH₃—CHCl—CH₂Cl and propylidene chlorohromide CH₃—CH₂—CHBrCl, while isopropylidene iodide would be (CH₃)₂CI₂.

The ethane derivatives are occasionally labeled according to another method. Symmetrical (sym.) dichloroethane is an alternative name for ethylene chloride and unsymmetrical dichloroethane is ethylidene chloride. Since the student may at any time be confronted with any of these types, it is necessary for him to be familiar with them.

Physical Properties.—The substitution of halogen for hydrogen gives substances with higher melting and boiling points, specific gravity, and refraction. A few of them are gases but most are liquids or, if the molecular weight is high or if there are several atoms of halogen, solids. Many of them are combustible to burn with a green or blue flame, especially on copper oxide as in the Beilstein test for halogen. All are difficultly soluble in water but easily soluble in alcohol or ether and usually in other common organic liquids. The more volatile often possess a pleasant odor and taste, although these become less marked with higher molecular weight and consequent decreased volatility. Inhalation of the lower derivatives by animals brings about analgesia and anesthesia.

Preparation.—1. All of them can be obtained by halogenation, as was explained previously, but it is difficult to separate the conglomerate mixtures so obtained except when made from methane. Therefore, this method is not generally a useful one unless one wishes to replace all hydrogen or unless the process can be controlled in other cases.

The halogen derivatives can be conveniently prepared by four other common methods. All of them involve the use of raw materials, the properties of which have yet to be considered, so that we will merely state them here without detailed discussion.

2. Addition of free halogen or of hydrohalogen to unsaturated compounds. (Chapter V.)

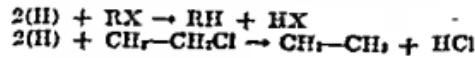
3. Action of hydrohalogens or non-metallic halides, such as phosphorus pentachloride, on the corresponding alcohols. (Chapter VI.)

4. Interaction of alkyl halides with metallic halides (see reactions).

5. Heating of amine salts. (Chapter XVII.)

Reactions.—In all of the halogen derivatives the substituted atom is not ionized and, even if soluble in water, the compounds cannot be precipitated by silver nitrate unless previously decomposed. One might conclude that the halogen is much more firmly bound than in inorganic salts, although actually we find that it is more or less slowly exchangeable in a number of directions. Indeed, the reactivity of this atom makes its compounds of immense importance in organic chemistry, largely as intermediates for the production of more valuable substances. A striking evidence for this ease of transformation is the fact that many of the compounds are decomposed in air or sunlight, especially those containing iodine. In general, it may be stated that the combined iodine atom is most easily replaced, the fluorine least.

1. Nascent hydrogen by "inverse substitution" yields the parent hydrocarbon.



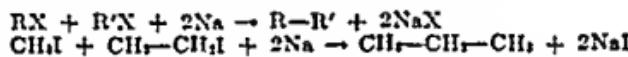
This may be accomplished in acid solution by metals like zinc, iron, or tin; in water by sodium or its amalgam; by means of electrolytic hydrogen; by catalytic activation of ordinary hydrogen, using finely divided metals like palladium, platinum, or nickel. The reduction is often performed by heating with a strong solution of hydrogen iodide, to which may be added a little phosphorus.



Since this is a reduction, it makes a good illustration of the difficulty of reducing a hydrocarbon.

2. Metals. The choice of metal depends on the metal used and on the physical conditions. A more detailed discussion about some of these reactions will be found in Chapter XX. There are three usual types although reactions in other ways are sometimes encountered.

(a) Wurtz Reaction.—This is used to produce hydrocarbons from halides of those with fewer atoms of carbon and is particularly useful for getting combinations of similar radicals. The process consists of treating the halide or mixture of two such compounds in ethereal solution with the metal. For this purpose sodium is generally employed, but zinc, magnesium, copper, or silver can be used if finely divided.

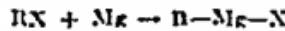


Also produced simultaneously are R—R and R'—R', and if the boiling points are far enough apart the three products may be separated by simple distillation. If a single halide is subjected to this treatment there is, of course, but one normal product. With higher derivatives it may be necessary to heat the reagents together or even to fuse them.

An illustration of the Wurtz reaction will make clearer the points made. Normal pentane can be obtained by treating with sodium a mixture of ethyl and n-propyl iodides. Simultaneously we also get n-butane and n-hexane which can hardly be separated from the desired pentane, may more than we can efficiently fractionate the components of petroleum. On the other hand, a mixture of n-hexyl iodide and methyl iodide would be a good source for n-heptane, boiling at 98°, since the other products ethane and n-decane have boiling points of -84° and 214° respectively.

When two or more halogen atoms are present in the compound, we may get by this method unsaturated or cyclic substances (see next chapter).

(b) Grignard Reagent.—Magnesium (less conveniently zinc or other metals) reacts with the halide in anhydrous ether solution to give an additive compound.



which is known collectively as the Grignard reagent. It adds to a great variety of unsaturated compounds to yield new substances which are still types of the reagent with just a larger radical.

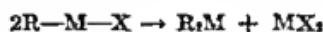


The products, including the simple R—Mg—X, decompose readily with water.



The Grignard reagent has become an extremely useful means of synthesis, because the radical in it can be increased almost at will to give final products of many classes. For a summary and extension of these see Chapter XX.

(c) The third type of reaction (Frankland) with metals is an older modification of the Grignard reagent, using zinc and other metals. There is first similarly an addition product R—M—X which will sometimes decompose with water as does the magnesium compound. The end reaction, however, is obtained by distilling the reagent to give metal derivatives of the alkyls or metal alkides.



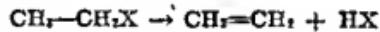
The same result may be gained directly by heating together the metal and alkyl halide. Zinc alkides were formerly much used in synthesis because they behave very much like the Grignard reagent, but they are no longer often employed because they are less convenient.

3. The halogen compounds are slowly decomposed by metallic hydroxides in aqueous solution to give alkyl hydroxides or alcohols.



As one could expect, iodides are most easily affected thus, fluorides least. Alkalies are naturally most efficient but have the disadvantage of giving extensive side reactions, so that milder agents are usually preferred. The usual method is to shake the halide with aqueous suspensions of silver or lead oxide. Even water alone will often accomplish the purpose and this may be facilitated by adding mineral acids or raising the temperature. In any event, the halogen atom is eventually replaced by hydroxyl, and this represents a useful and simple process for making oxygen substitution products.

If the aqueous base is replaced by an alcoholic solution the result is quite different, although probably by merely acting on the hydroxyl group further. Attainment of the final result may be stated as removal of hydrohalogen, which is neutralized by the base, and production of an unsaturated hydrocarbon. (Chapter V.)



In this reaction iodides again react most easily, fluorides least, while those halogens attached to tertiary carbon are more readily affected than if to a secondary or primary carbon. This removal of hydrohalogen can also be accomplished by other bases such as ammonia and its derivatives, like pyridine or the alkaloids. Heating with lime or other metallic oxides, or even beating alone or with catalytic agents, will often be successful.

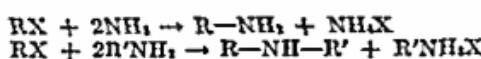
4. Metal salts of inorganic or organic acids react at higher temperatures by double decomposition, as do also many organic compounds containing the metals.



Some examples of the varied nature of A are CN (cyanide), ONO (nitrite), ONO_2 (nitrate), and OR (alkoxy).

An interesting application of the process is the preparation of certain alkyl halides by double decomposition with inorganic salts. The fluorides are best made in this manner, using antimonous fluoride or sodium fluoride. Mercuric, hydrogen, or stannic chlorides react with alkyl bromides or iodides; while aluminum bromide will decompose chlorides; and sodium, calcium, or fuming hydrogen iodides, boiled in alcohol or acetone, will react with bromides or chlorides.

5. The alkyl halides will add to ammonia or its derivatives (amines) in the process of alkylation (Chapter XVII). If this is carried out under pressure the halogen atom may be replaced by a nitrogen group.



Compounds.—A few of the halides which are used in medicine or are important in other ways are listed herewith, together with some of their characteristics. For further details or additional properties the student is referred to descriptions given elsewhere.

Methyl Chloride or Chloromethane is a colorless gas boiling at -24° and is quite poisonous if inhaled. It is used as a freezing agent to produce local anesthesia and as a refrigerant in household appliances.

Ethyl Chloride U.S.P. (Kelene N.N.R., Chloroethane) is a colorless liquid boiling at 12° and having a specific gravity of 0.918. It is administered as a local anesthetic from an atomizer and is sometimes inhaled as a general anesthetic.

Chloroform U.S.P. (Methenyl Chloride, Trichloromethane) is a colorless liquid boiling at 61° . Besides its known application as anesthetic, it finds other uses in medicine, as attested by the popular water, spirit, and liniment.

Iodoform N.F. (Methenyl Iodide, Triiodomethane) is a yellow solid with a peculiar, persistent odor and melting at 119° . In spite of many so-called substitutes iodoform is still used for its local action on wounds.

Carbon Tetrachloride U.S.P. (Tetrachloromethane) is a colorless liquid boiling at 77° . It is a remedy for worms and a popular fire-extinguisher and cleaning solvent.

Chlorinated Paraffin N.F. (Chloreosane) is used as a solvent for Dichloramine-T.

Methyl bromide is said to have advantages over carbon tetrachloride as a fire-extinguisher and it is also used as an insecticide. Ethyl bromide and ethyl iodide have been employed as anesthetics and are useful in syntheses. Bromoform, CHBr_3 , is used in medicine like the organic bromides. Methylene iodide is the heaviest of all organic liquids, having a specific gravity of 3.3, and is valuable for this property in a number of ways. Methylene chloride is an official reagent.

Ethylene dichloride, $\text{CH}_2\text{Cl}-\text{CH}_2\text{Cl}$, or Dutch Liquid, boils at 84° and has a specific gravity of 1.26. It is one of the most stable of halogenated hydrocarbons now available and finds an immense number of uses in industry as a solvent. The isomeric ethyldene chloride, boiling at 58° , is used as insecticide. Sym-tetrachloroethane, $\text{CHCl}_2-\text{CHCl}_2$, is an industrial solvent, while hexachloroethane is employed in fireworks. Dichlorodifluoromethane, CCl_2F_2 , is a non-inflammable, non-toxic, and non-corrosive refrigerative medium (Freon).

REVIEW QUESTIONS

1. Write formulas for methylene bromide, ethyldene chloride, methenyl iodide, ethylene chloride, 2-methyl-3-chloropentane, tertiary-butyl iodide, α , β -dibromobutane, symmetrical-dichloroethane.
2. Why is halogenation not efficient to prepare halides?
3. State three other methods used to prepare them.
4. Which of the halogens in these reacts most readily?

5. How do the halides react to reduction? Write equations. With what agents can this be accomplished?
6. What is the Wurtz reaction? Write equations to illustrate.
7. What is the Grignard reagent? How does it behave with water? Write equation.
8. How are the metal alkyls or alkides prepared? Write equation.
9. How do the halides behave with aqueous metal hydroxides? Which one is usually used? Write equations.
10. Write equations for heating the halides with sodium nitrate and with sodium cyanide (NaCN).
11. Write equation for heating alkyl halides with ammonia under pressure.
12. Give chemical names to chloroform and iodoform and write formulas.
13. Which of the other paraffin halides are official?
14. What is chloroosane? For what is it used?

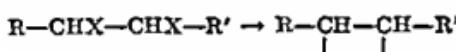
CHAPTER V

UNSATURATED HYDROCARBONS

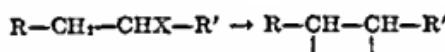
As an introduction let us review three reactions that we noted in the last chapter.

1. When a monobalide is treated with a metal, the halogen atom can be removed (Wurtz). $\text{RX} + \text{M} \rightarrow \text{MX} + \text{R}\cdot$. The radical thus set free cannot exist independently but must unite with more metal to form alkides or with itself to form higher homologues. $2\text{R}\cdot \rightarrow \text{R}-\text{R}$.

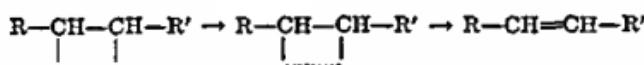
2. When a dihalide is treated in the same way, we could get a divalent radical.



3. When a monohalide is treated with alcoholic alkali, hydrohalogen is withdrawn to form a like radical if there is a hydrogen atom linked to an adjacent carbon atom.



In either of the last two cases we found that an unsaturated compound is formed. The radical might perhaps be expected to unite with itself just as in the Wurtz reaction, but instead the two free linkages satisfy each other.



We now have two bonds between a pair of carbon atoms, or a "double bond."

If a compound with two halogen atoms linked to the same carbon was treated with a metal, we would still arrive at the double bond through union of two radicals so formed.

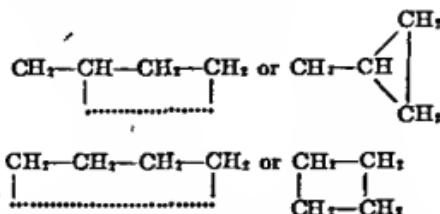


There could be obtained thus by any of the three methods a whole series of compounds each containing a double linkage and obviously two hydrogen atoms less than the paraffin with the same number of carbon atoms. The general formula of the class would be C_nH_{2n} , which is C_nH_{2n+2} minus 2 atoms of hydrogen. Isomerism due to position of the double bond makes the total number of possibilities far greater than in the methane series. While there is only one corresponding to ethane and one to propane, three of them have 4 carbon atoms and are related to the two butanes. They are $\text{CH}_3-\text{CH}_2-\text{CH}=\text{CH}_2$, $\text{CH}_3-\text{CH}=\text{CH}-\text{CH}_3$, and $(\text{CH}_3)_2\text{C}=\text{CH}_2$. Analogously there are five from the three pentanes and thirteen from the five hexanes. The student should derive all of these so that he will thoroughly understand the structure.

It may have been noted that abstraction of the two hydrogens from carbon atoms which are not adjacent is still another possibility. Applying the same system of preparation, we arrive at quite different results. If we

remove with sodium two halogen atoms from 1,2-dibromobutane or from 2,3-dibromobutane, it is equivalent to abstracting two atoms of hydrogen from butane and gives $\text{CH}_3-\text{CH}_2-\text{CH}=\text{CH}_2$ and $\text{CH}_3-\text{CH}=\text{CH}-\text{CH}_3$, respectively. But if we abstract the two hydrogens from the 1,3 and 1,4 positions, we would get $\text{CH}_3-\overset{\text{CH}_2}{\underset{\text{CH}_2}{\text{CH}}}-\overset{\text{CH}_2}{\underset{\text{CH}_2}{\text{CH}}}_2$ and $\overset{\text{CH}_2}{\underset{\text{CH}_2}{\text{CH}}}-\overset{\text{CH}_2}{\underset{\text{CH}_2}{\text{CH}}}_2-\text{CH}_2$ —

CH_2 . Union of the free bonds would then give



The ring or cycle so formed is characteristic of other series of hydrocarbons, the discussion of which will be postponed.

It must be emphasized, however, that removal of 2 hydrogen atoms from members of the saturated series may lead only to a double bond if at adjacent carbons, or to a cycle if at carbons not adjacent. Conversely, any double bond or ring in a hydrocarbon shows 2 hydrogen atoms less than the corresponding paraffin.

OLEFINES

Nomenclature.—Members of the series containing a double bond are called alkynes, ethenes, ethylenes, or most often olefines. The reasons for these will be apparent as we proceed. The compounds were originally named by putting —ylene in place of —ane in the related paraffin, but this is impractical in the bigger compounds, because of isomerism due to position of the double bond. For instance, the three derived previously from the butanes would all then be butylenes. While we might call the branched one isobutylene, the others would both be normal butylenes.

A second system of naming is similar to the one for the paraffins which considers the latter as derivatives of methane. The radical methylene is apparently incapable of independent existence, so we look upon the olefines as derived from the first member, ethylene.

$\text{CH}_3-\text{CH}=\text{CH}_2$	propylene or methylethylene
$\text{CH}_3-\text{CH}=\text{CH}-\text{CH}_3$	sym-dimethylethylene
$\text{CH}_3-\text{CH}_2-\text{CH}=\text{CH}-\text{CH}_3$	sym-ethylmethylethylene
$(\text{CH}_3)_2\text{CH}=\text{CH}_2$	isopropylethylene

This system is satisfactory again until the radical becomes too complicated.

In the Geneva method the double bond is indicated by the suffix "ene" and its position by a number. For this purpose carbon 1 is selected at the end closer to the double bond, and the number used for the latter is the lowest of the two carbons that it connects. The formulas last written are in order: propene; 2-butene; 2-pentene; 3-methyl-1-butene. As long as the double bond can be included in the longest chain this system of naming is entirely satisfactory; if necessary we may select a shorter chain so as to include it. The double bond may also be indicated by a prefixed Greek Δ , followed by number for position. In this way 2-butene becomes Δ^2 -butene and 3-methyl-1-butene becomes 3-methyl- Δ^1 -butene.

Physical Properties.—Physically the olefines differ only in degree from hydrocarbons of the methane series. The boiling points and refractions are higher and there are general increases or decreases in constants with changes in molecular weight. There is, however, the same gradation in physical properties as the number of carbon atoms grows larger, the lower ones being gases and the higher ones liquids and solids. The solubilities are closely comparable with those of the saturated series.

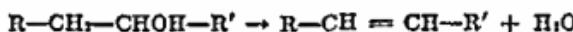
Preparation.—The compounds containing a double bond are commonly made by several methods, some of which cannot be discussed in detail at this point.

1. In the first of these the alkyl halides are treated with alcoholic bases to remove hydrohalogen, as was explained earlier.



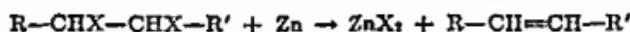
The same effect can often be obtained by heating with lime or litbarge and sometimes by simple distillation.

2. An analogous method removes water from hydroxyl derivatives by means of dehydrating agents.



The substances used for this purpose include sulfuric acid, phosphorus pentoxide, zinc chloride, syrupy phosphoric acid, hot clay or aluminum oxide, and anhydrous formic acid.

3. Similarly they may be made by removing two neighboring atoms of halogen by means of zinc or other metals, as has been suggested before.

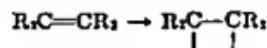


4. Electrolysis of certain salts is sometimes a very convenient method. (Chapter XII.)

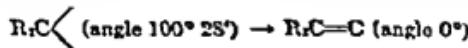
5. From acetylenes by hydrogenation. (This chapter.)

6. The most useful process on a commercial scale is from the higher paraffins by cracking. Using materials from crude petroleum, quite a number of the olefines are now obtained by this treatment, either for direct marketing or as intermediates in the production of more valuable compounds, chiefly alcohols. The olefines also occur as products from distillation of shales, some kinds of coal, and various other materials.

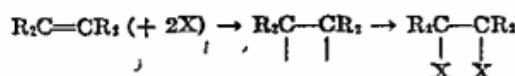
Reactions.—Unlike the paraffins, the olefines are very reactive. The double bond, instead of being a source of strength as one might expect, is easily disrupted to produce a single one and two free valences which can combine then with reagents.



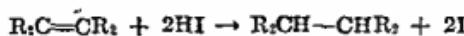
The strains, which might be produced (Baeyer) by altering normal directions of two valences from carbons to yield a double bond, can best be appreciated after reference to models. On the plane of the paper it can be represented as follows:



Each linkage must, therefore, be changed (strained) through one-half of $109^\circ 28'$ or $54^\circ 44'$. Many substances on mere contact will relieve this strain by uniting with the bonds.



1. The olefines will thus add nascent hydrogen to form paraffins; used for this are sodium amalgam and water, zinc and acid or even water at 160° , sodium alcoholate, or the copper-zinc couple. The reduction may be accomplished by heating with concentrated hydriodic acid and a little red phosphorus.



Ordinary hydrogen will also add at elevated temperatures under the influence of catalysts which absorb it, such as nickel, platinum, or palladium.

2. The halogens will saturate the double bond to give dihalides of the paraffin series.



Chlorine adds more easily than bromine, which is in turn more active than iodine. In general bromine water will react in the cold with the gaseous olefines; indeed, the disappearance of bromine color is used as a test for the double bond. It should be noted that some compounds do not add halogen in spite of the presence of a double bond; *e. g.*, isobutylene.

3. The hydrohalogens will also add, hydrogen chloride being the least and hydrogen iodide the most active. Since here we have two unlike atoms to combine, position for each must be noted. The rule (Markownikoff) is that the negative element or radical, in this case halogen, goes to that carbon atom that is connected to the least hydrogen; *i. e.*, the carbon atom that is most differentiated. It should be noted that this rule applies to hydrocarbons but may be different with other compounds as we shall see later. With propene, $\text{CH}_3-\text{CH}=\text{CH}_2$, we get $\text{CH}_3-\text{CHCl}-\text{CH}_3$, and not $\text{CH}_3-\text{CH}_2-\text{CH}_2\text{Cl}$. This furnishes a convenient means for changing the position of a halogen atom; if we remove hydrogen iodide from n-propyl iodide to produce propene, we can now add it again and get isopropyl iodide.

4. While water cannot be added directly to give hydroxyl compounds, the same purpose may be accomplished by adding acid, as in 5, and hydrolyzing the resultant ester (Chapter VII). The process is of great importance for the preparation of alcohols from products of cracking petroleum.

5. Acids in general will saturate the double bond, but the ease with which this goes on depends on the nature of both acid and olefine. Fuming sulfuric acid absorbs ethylene at room temperature, while the ordinary concentrated acid does so only at 160° to 170° . Some organic acids require much higher temperatures, but the reactions in many cases can be enhanced by certain catalysts.

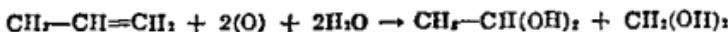


Hypohalous acids form so-called halohydrins, a useful method in synthesis.



It will be noted that the OH or negative group goes to the carbon having the least hydrogen.

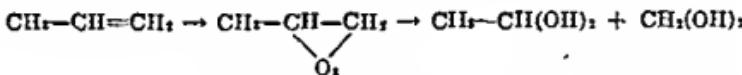
6. Oxidizing agents in general split both bonds to disrupt the molecule



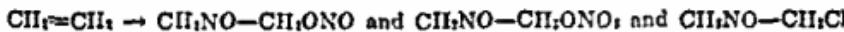
With diluted potassium permanganate in alkaline solution, however, only one bond is usually severed to give a dihydroxyl compound



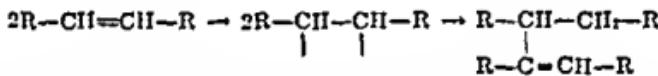
Like the test with bromine, disappearance of the purple color is taken for evidence of a double bond (unsaturated). Ozone adds itself at the double bond to give ozonides, which decompose with water to yield products like other oxidizing agents.



7. Other reagents which may be added are nitrogen trioxide to give nitrosonitrites (nitrosites), nitrogen tetroxide to give nitrosonitrates (nitrosates), and nitrosyl chloride to form nitrosochlorides.



8. The additive capacity of olefines is so great that, even if placed with no reagents, they often add in themselves, forming usually new compounds of higher molecular weight.



Sometimes many molecules unite together in this way to give complicated compounds. This process of combining like molecules, which is called polymerization, is quite common with all substances containing a double bond, whether hydrocarbon or not.

Ethylene U.S.P. (Ethene, Olefiant Gas) is a gas which was introduced in 1921 as a general anesthetic and has since become exceedingly popular. It is also used to ripen fruit (*e. g.*, citrus) rapidly. The name olefiant (oil forming) gas or olefine, which gives a general title to the whole series, arises from the fact that ethylene unites with chlorine to form Dutch liquid or ethylene chloride, a heavy oil. The chief objection raised to its general application as anesthetic is its great inflammability and tendency to explode when mixed with the requisite amount of air. Propylene, a similar gas, has also been proposed and used as anesthetic.

Although each of these olefines can be made in several ways, they are produced today in immense quantities by the cracking of higher hydrocarbons in the petroleum industry. They are mainly used to furnish other derivatives, and it is said that more than fifty products are obtained from ethylene alone.

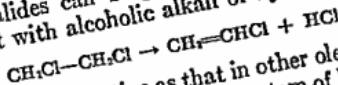
"Pental" is a mixture of two pentenes obtained from fusel oil by dehydration with zinc chloride and also by cracking petroleum. They are 2-methyl-2-butene and 2-methyl-1-butene,



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also called β -isoamylene and γ -amylene respectively. Both of these compounds give the same product on hydration, amylene hydrate, $\text{CH}_2-\text{COH}(\text{CH}_3)-\text{CH}_3$.

Halogen Derivatives.—Monohalogen substitution products of ethylene are compounds of the monovalent radical, $\text{CH}_2=\text{CH}-$, which is called vinyl. The vinyl halides can be prepared from ethylene or ethyldene halides by treatment with alcoholic alkali or by simple heating,

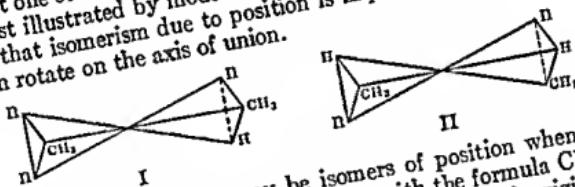


The double bond is just as reactive as that in other olefines and polymerization takes place with very great ease, but the atom of halogen is surprisingly stable. Indeed, it may be stated generally that halogen in the combination $=\text{CHX}$ is extremely resistant to action of reagents. In the combination $\text{CH}_2=\text{CH}-\text{CHX}$, for example, it is just as unreactive. In propenyl, the isomeric allyl compounds, $\text{CH}_2=\text{CH}-\text{CH}_2\text{X}$, the halogen has in usual properties and even to a greater degree.

Trichloroethylene U.S.P., $\text{CHCl}=\text{CCl}_2$, is a liquid that is used by inhalation for analgesia, especially in trigeminal neuralgia. It is a very useful solvent in industry.

Tetrachloroethylene U.S.P., $\text{CCl}_2=\text{CCl}_2$, is a non-inflammable liquid with an ethereal odor. It is employed as a vermifuge for the hookworm.

Geometric Isomerism (Allo-isomerism).—In a molecule of *n*-butane, $\text{CH}_3-\text{CH}_2-\text{CH}_2-\text{CH}_3$, the bond between carbons 2 and 3 is of such a nature that one of them can be rotated while the other remains stationary. This is best illustrated by models where I can be changed to II and back again, so that isomerism due to position is impossible because the carbon atoms can rotate on the axis of union.

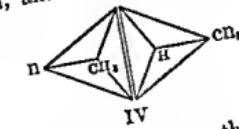


II

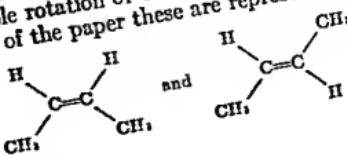
On the other hand, there may be isomers of position when a double bond is present. There are two compounds with the formula $\text{CH}_2=\text{CH}-\text{CH}_2-\text{CH}_3$, 2-butene, the explanation of which rests on the rigidity of the double linkage as contrasted with the flexibility of a single one. Again the models will aid in making this clear; the two formulas represented by III and IV cannot be superimposed, and the second cannot be altered



III



to give the first without disruption of bonds, because the two points of union make impossible rotation of either carbon atom in reference to the other. On the plane of the paper these are represented as

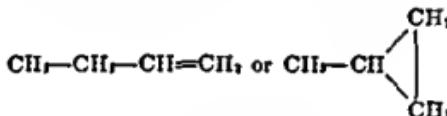


This brand of stereo-isomerism is called geometric or allo-isomerism. The examples given represent the general formula $R-C(R^1)=C(R^2)R^3$ in which R and R^1 must be different, also R^2 and R^3 , although R may be identical with R^2 and also R^1 with R^3 and either pair may be elements, including hydrogen. The two compounds are distinguished by the prefixes cis- and trans-; for our illustrations the names become cis-2-butene and trans-2-butene. In other cases the common one is called by the chemical name and the other is designated by the prefix allo-; the geometric isomer of cinnamic acid is known as alloeinnamic acid. Again it is sometimes customary to give each a different name. The two compounds with the formula HOOC-CH=CH-COOH are called maleic acid or cis-ethylenedicarboxylic acid and fumaric acid, trans-ethylenedicarboxylic acid, or allomaleic acid.

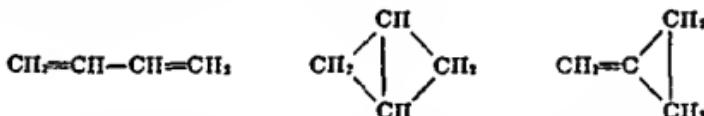
DIOLEFINES OR ALLYLENES

If we abstract another pair of hydrogen atoms from the formula C_nH_{2n+2} we obtain C_nH_{2n-2} . This can be done by chemical means, as has already been described in removing the first two atoms to produce the olefines. The product would contain another double bond or another ring, or one of each, depending on where the second pair is withdrawn.

Starting with n-butane, we could get for the first pair as representative compounds



For the second pair there could be produced

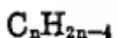


representing two double bonds, two rings, and one of each respectively. Postponing any discussion of cyclic compounds, we need to mention here only the diolefines, characterized by two double bonds. These compounds are given common names and are also designated by the Geneva system, using "diene" to indicate the double bonds and two numbers to indicate positions. 1,4-diene would be $\text{CH}_2=\text{CH}-\text{CH}_2-\text{CH}=\text{CH}-\text{CH}_2$.

As would be expected, few new properties are encountered in this series. Each of the double bonds acts more or less independently, so that the compounds are more unstable than the olefines and can add reagents in double the quantity. However, when we have a conjugated system of alternate single and double bonds as in butadiene, $\text{CH}_2=\text{CH}-\text{CH}=\text{CH}_2$, treatment with reagents often results in so-called 1,4 addition. Bromine, for example, gives $\text{CH}_2\text{Br}-\text{CH}=\text{CH}-\text{CH}_2\text{Br}$ instead of $\text{CH}_2=\text{CH}-\text{CHBr}-\text{CH}_2\text{Br}$ which might be predicted as first product.

Since compounds containing one or more double bonds are unstable and very easily polymerized, several of them have recently become quite prominent in the manufacture of so-called "artificial rubber." Among the most important of these is butadiene, also called pyrrolene, crythrene, or divinyl. It boils at about -5° but can be compressed to a liquid at room

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1. $\pi\pi\pi$
2. $\pi\pi\Delta$
3. $\pi\Delta\Delta$
4. $\Delta\Delta\Delta$
5. $\Sigma\pi$
6. $\Xi\Delta$

Triolefines }
Terpenes }



1. $\pi\pi\pi\pi$
2. $\pi\pi\pi\Delta$
3. $\pi\pi\Delta\Delta$
4. $\pi\Delta\Delta\Delta$
5. $\Delta\Delta\Delta\Delta$
6. $\Sigma\pi\pi$
7. $\Sigma\pi\Delta$
8. $\Sigma\Delta\Delta$
9. $\Xi\Sigma$

Tetraolefines
Benzene and homologues



1. $\pi\pi\pi\pi\pi$
- etc.

Pentaolefines

REVIEW QUESTIONS

1. Define alkylene, alkene, olefine.
2. In what two ways can olefines be made from halides? How from alkyl hydroxides? Write equations.
3. What is the general formula of the series?
4. Derive the possible olefines containing 5 carbon atoms and name each as a derivative of ethylene and by the Geneva system.
5. How are the olefines made commercially?
6. What is the chief chemical property of olefines?
7. Write equations to illustrate addition of hydrogen, hydrohalogen, halogeno, water, propene, oxidized with dilute potassium permanganate? equations using (O) for the agent.
8. What is meant by polymerization?
9. Write formulas of ethyleoee, vinyl chloride, propenyl bromide, allyl iodide, trichloroethylene, tetrachloroethyleoe. Which of these are used in medicine?
10. Define geometric isomerism. Illustrate, usiog 2-pentene. Name the two isomers
11. What is a diolefine? A triolefine? An acetylene?
12. Name divinylacetylene and isopropylmethylacetylene by the Geneva system.
13. Define unsaturated compound.
14. Write the formulas of isoprene and chloroprene.
15. Write equation for the action of methylacetylene on ammoniacal cuprous chloride.
16. What could be the possible structure of a compound, C_7H_8 ?

CHAPTER VI

ALCOHOLS

IN view of the fact that oxygen goes with carbon and hydrogen to make up most organic compounds, we will next consider substitution products containing this element. Although the monovalent halogen atom could displace but one atom of hydrogen, oxygen has twice the combining power and can displace two. However, instead of looking upon the important oxygenated substances as derived by exchanging two atoms of hydrogen for one of oxygen, the substituting group is best considered as the monovalent—OH. On a purely empirical basis, therefore, the replacement involves merely addition of one oxygen atom: $R-H + (O) \rightarrow R-O-H$. When this is done once the product is called an alcohol.

In the alcohols it is necessary to distinguish the position of substitution. A halogen atom imparts certain properties to a compound in which it occurs, practically regardless of its situation in the molecule, but there are three species of alcohols distinctly different in certain properties. As has been pointed out before, we have three kinds of groups containing a single atom of carbon: the primary $-CH_3$, attached by only one bond to another carbon atom; the secondary $-CH_2-$ connected by two bonds to one or two; and the tertiary $=CH$, attached by three bonds to one, two or three carbon atoms. Replacement of one hydrogen by hydroxyl in each of these gives primary, secondary, and tertiary alcohols respectively. Examples of each in order are CH_3-CH_2OH , $CH_3-CHOH-CH_3$, and $(CH_3)_2COH-CH_3$. Stated in another way, primary alcohols are characterized by $-CH_2OH$ and may be written generally $R-CH_2OH$; secondary, alcohols have the group $=CHOH$ and the general formula R_2CHOH ; tertiary alcohols have the group $=COH$ and the general formula R_3COH .

Nomenclature.—As with hydrocarbons, there are three methods of naming the alcohols and again the Geneva system is preferred in the more complicated compounds.

The first method simply names the radical in $R-OH$ or gives an empirical title. $CH_3-CH_2-CH_2OH$ is n-propyl alcohol and $CH_3-CHOH-CH_3$ is isopropyl alcohol, while amylene hydrate has been selected for $(CH_3)_2COH-CH_2-CH_3$.

In the second, attributable to Kolbe, one considers them as derived from the simplest, methyl alcohol, which is for this purpose called carbinol. The examples given then become in order ethylcarbinol, dimethylcarbinol, and ethyldimethylcarbinol. This is entirely analogous to that which views hydrocarbons as derived from methane.

In the Geneva system the hydroxyl group is designated by the suffix -ol, and the number for position follows or precedes this. For the three compounds cited we have propan-1-ol, propan-2-ol, and 2-methylbutan-2-ol. In some complex compounds it is permissible and often advantageous to use the prefix hydroxy-.

In the accompanying table are given the formulas, the three names in the same order as just discussed, and the class of some of the lower alcohols.

Formula	Names	Class
CH ₃ OH	methyl alcohol	primary
	carbinol	
	metbanol	
CH ₂ —CH ₂ OH	ethyl alcohol	primary
	methylcarbinol	
	ethanol	
CH ₃ —CH ₂ —CH ₂ OH	n-propyl alcohol	primary
	ethylcarbinol	
	propan-1-ol	
CH ₃ —CHOH—CH ₃	isopropyl alcohol	secondary
	dimethylcarbinol	
	propan-2-ol	
CH ₃ —CH ₂ —CH ₂ —CH ₂ OH	n-butyl alcohol	primary
	n-propylcarbinol	
	butan-1-ol	
CH ₃ —CH ₂ —CHOH—CH ₃	sec-butyl alcohol	secondary
	ethylmethylcarbinol	
	butan-2-ol	
(CH ₃) ₂ CH—CH ₂ OH	isobutyl alcohol	primary
	isopropylcarbinol	
	2-methylpropan-1-ol	
(CH ₃) ₂ COH—CH ₃	tert-butyl alcohol	tertiary
	trimethylcarbinol	
	2-methylpropan-2-ol	
CH ₃ —CH ₂ —CH ₂ —CH ₂ —CH ₂ OH	n-amyl (pentyl) alcohol	primary
	n-butylcarbinol	
	pentan-1-ol	
CH ₃ —CH ₂ —CH ₂ —CH ₂ —CHOH—CH ₃ *	methyl-n-propylcarbinol	secondary
	pentan-2-ol	
CH ₃ —CH ₂ —CHOH—CH ₂ —CH ₃	diethylcarbinol	secondary
	pentan-3-ol	
(CH ₃) ₂ CH—CH ₂ —CH ₂ OH	isobutylcarbinol	primary
	3-methylbutan-1-ol	
(CH ₃) ₂ COH—CH ₂ —CH ₃	tert-amyl alcohol	tertiary
	ethylidimethylcarbinol	
(CH ₃) ₂ CH—CHOH—CH ₃ *	2-methylbutan-2-ol	secondary
	isopropylmethylcarbinol	
CH ₃ —CH ₂ —CH(CH ₃)—CH ₂ OH*	3-methylbutan-2-ol	primary
	active amyl alcohol	
	sec-butylcarbinol	
	2-methylbutan-1-ol	
(CH ₃) ₂ C—CH ₂ OH	tert-butylcarbinol	primary
	2,2-dimethylpropan-1-ol	

It will be observed that, of the eight amyl (pentyl) alcohols, the three marked with an asterisk contain asymmetric carbon atoms and, hence, exist each in dextro, levo, and racemic forms. The higher alcohols show an increasing number of isomers. There are 17 hexyl and 38 heptyl alcohols, and optical isomerism adds many more.

Physical Properties.—The lower members of the series are colorless, inflammable liquids with characteristic odor and possessed of a burning taste, while the higher ones are waxy solids. The solubility in water of the first four is unlimited, but this property alters as the molecular weight increases. The amyl alcohols and those with more carbon atoms dissolve in water to a very limited extent or practically not at all. As was observed

with the hydrocarbons, the normal compounds have the highest boiling points, those with most branching the lowest.

Preparation.—1. **Hydrolysis of Esters:** While we have yet to consider the esters, we have already noted a type of this process. The halides are converted to alcohols by treatment with aqueous alkali, with moist silver or lead oxide, or even sometimes with water at 100°. Iodides are readily so affected, bromides and chlorides less easily.

2. The olefines were found to hydrate with water under certain conditions. This is best carried out with acids as the hydrating agents, and esters are then obtained as intermediate products. In this way isopropyl, tertiary butyl, and other alcohols are produced in large quantities as by-products of the processes used in the cracking of petroleum.

The other prominent methods are merely listed and discussion of them is postponed until we come to a consideration of the raw materials indicated.

3. Reduction of aldehydes, ketones, esters, and other derivatives of acids. (Chapters IX, X, XII.)

4. From primary amines by reaction with nitrous acid. (Chapter XVII.)

5. From aldehydes and ketones by means of the Grignard reagent. (Chapters IX, X, XX.)

6. Catalytically from carbon monoxide (see methanol).

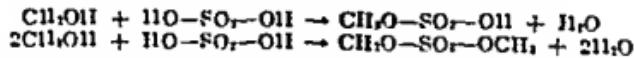
Reactions.—1. Some of the lower ones combine with inorganic salts as alcohols of crystallization, just as does water. Typical compounds are $\text{CaCl}_2 \cdot 4\text{CH}_3\text{OH}$, $\text{CaCl}_2 \cdot 4\text{C}_2\text{H}_5\text{OH}$, and $\text{MgCl}_2 \cdot 6\text{CH}_3\text{OH}$. Because of such combinations, calcium chloride cannot always be used as a drying agent by direct contact with liquid mixtures containing alcohols.

2. The hydroxyl group is theoretically analogous to the same structure in inorganic chemistry and might be expected to show acid and basic properties. Although the alcohols usually furnish neither hydrogen nor hydroxyl ions, they actually do behave in some respects like acids and bases. With inorganic bases *they do not generally form salts*, but some of them liberate hydrogen when treated with active metals like sodium or potassium.



Some of the primary and secondary alcohols give similar compounds with lime or barium at higher temperatures. The resulting alcoholates are decomposed readily by acids, even by such weak ones as carbonic, and plain water will usually hydrolyze them completely.

3. On the other hand, alcohols will react with acids to form esters which are analogous to inorganic salts. Thus, with sulfuric acid, we may get normal and acid sulfates



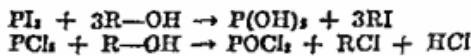
While the primary and secondary alcohols can thus be esterified quite easily, the tertiary compounds are frequently resistant to any change. For hydroiodic acid see 5.

4. The halogen substitution products may be regarded as esters of the corresponding hydrohalogen acids, and the simpler ones can be prepared

by reaction of the alcohol with the hydrohalogen, especially with a dehydrating agent present.



Here we find that tertiary alcohols are converted most easily, primary with most difficulty. The simplest and usual method of preparation from hydroxyl compounds, however, is by warming the latter with halides of phosphorus.

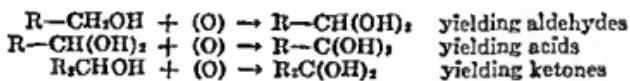


For this purpose the trihromide and triiodide of phosphorus are sufficient, as are also sometimes a mixture of red phosphorus and the halogen. Thus, methyl iodide is easily manufactured by warming a mixture of red phosphorus, iodine, and methyl alcohol. Phosphorus pentachloride will change hydroxyl groups to chlorine and is the most useful general agent for the purpose, but the trichloride almost always produces alkyl esters of phosphorous acid, $(\text{RO})_3\text{P}$.

5. Any alcohol can be reduced by means of hydrogen iodide to the parent hydrocarbon because it is first converted to the iodide. Other reducing agents, such as nascent hydrogen, are not effective.

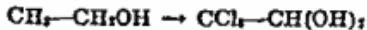


6. Primary and secondary alcohols are readily oxidized to dihydroxy and trihydroxy compounds. The direct oxidation of hydrocarbons to alcohols is impracticable because any agent powerful enough to bring this about will certainly be more than sufficient to carry the process further. However, it might be noted parenthetically that such an oxidation to alcohols has been found possible on the commercial scale if certain catalytic agents are used. Once a hydroxyl group is attached to a carbon atom, any other hydrogen atoms on this same carbon atom can be changed by mild agents to other hydroxyl groups. This is, of course, true only of primary and secondary alcohols.



Tertiary alcohols, like hydrocarbons, can be oxidized only by disrupting the molecule.

Halogens, which are good oxidizing agents, may thus react and may also substitute for hydrogen in hydrocarbon radicals, but not for that in the hydroxyl group. Thus, ethyl alcohol by chlorine is both oxidized and chlorinated.

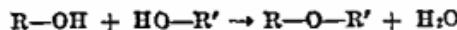


Under such circumstances the hydrogen of $-\text{CH}_2\text{OH}$ or of $=\text{CHOH}$ is not substituted but oxidized by the halogen, although halogenation goes on in another part of the molecule.

7. Dehydration of alcohols may take place in two different directions, each under a given set of conditions. In one a molecule of water is removed between the hydroxyl group and a hydrogen attached to a neighboring carbon atom to produce unsaturation.

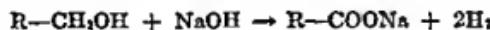


In the other the water is abstracted from the hydroxyl groups of two molecules to produce an oxide or ether.

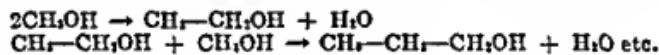


The conditions favoring each of these two processes will be considered in the next chapter. The dehydrating agents that have been used are quite numerous. Sulfuric acid, most popular in the laboratory, has the disadvantage of being partly reduced to sulfur dioxide. Benzenesulfonic acid is free from this handicap. Also employed are phosphorus pentoxide, syrupy phosphoric acid at higher temperatures, hot clay or aluminum oxide, zinc chloride, formic acid, boron oxide, oxalic acid, and even hot hydrogen chloride in a sealed tube. Tertiary alcohols often dehydrate to olefines without any such agent at slightly elevated temperature.

8. Certain of the primary alcohols will react under thermal conditions with caustic alkalies to yield salts and hydrogen.



Methyl alcohol (carbinol, wood alcohol, wood spirit, methanol, methyl hydroxide, Columbian spirit) is described as an official reagent. It occurs naturally in many plants, often in the form of glycosidal esters, and is obtained together with acetone and other compounds by the dry distillation of wood, beet vinasse, and other plant materials. It is also made by synthesis with a catalyst from carbon monoxide and hydrogen at about 400° and 150 atmospheres of pressure. The product of the latter process, which is becoming of great importance in industry, is usually referred to as methanol. The catalytic process from carbon monoxide just described can be modified to produce higher normal alcohols. This is accomplished by reducing the rate of passing the mixed gases and by changes in pressure. The reactions are presumed to be as follows:



Methyl alcohol is much used as antifreeze, as fuel, as solvent, and as denaturant of grain alcohol.

Alcohol U.S.P. (Ethyl or grain alcohol, ethanol, wine or Cologne spirit) contains about 92 per cent by weight of $\text{CH}_3-\text{CH}_2\text{OH}$ with water, or 95 per cent by volume. The stronger (dehydrated) and weaker (diluted to about 50 per cent) are also official. Alcohol may be made by the synthetic methods already noted, chiefly from ethylene, acetylene, or carbon monoxide, but is usually manufactured by fermentation of sugars by yeast or indirectly of cereals, wood, or straw. The change of dextrose to alcohol under the influence of zymase from yeast may be represented by the equation



This reaction is retarded by excessive alcohol so that it is self-limiting;

Spirituous liquors vary in properties with the raw materials, with the content of alcohol, and with the process used after fermentation. They

are roughly divided into three groups: malted, vinous, and distilled. The first, obtained from cereals by the action of malt previous to treatment with yeast, includes the beers, ales, porters, and stouts. The wines are obtained by direct fermentation of natural sugars as contained in fruits, especially the grape. The wine is said to be dry when most of the sugar has been fermented and sweet when there is an excess of sugar or more has been added. The product may be fortified by incorporation of additional alcohol, as in sherries and ports. Any of these alcoholic liquors may be distilled to give so-called hard liquors or for the purpose of preparing purer alcohol. Since separation of alcohol and water by simple distillation is an inefficient process, resort is usually made to the dephlegmator or fractionating column, and this method has been improved so much that an almost pure alcohol can now be so made. Gin from juniper berry, rum from molasses, whiskies from cereals, and brandy from wine are the most important distillation products besides pure alcohol. Whisky U.S.P. and Brandy U.S.P. are sometimes used in medicine.

In many of the alcoholic beverages the water and alcohol are accompanied by other substances from the fermentation. The differences in flavor are due to the presence of one or more of these in varying quantity. The most important are esters, ethers, aldehydes, glycerin, and fusel oil.

Pure alcohol is a colorless, volatile liquid with a characteristic odor and burning taste and boils at about 78° . It burns readily with a blue flame, even after addition of some water. Dilution much below a strength of 50 per cent, however, renders it non-inflammable. That hydroalcoholic liquor which will just burn enough to ignite a mixture with gunpowder and which is called proof spirit, contains about 50 per cent by volume of alcohol. This is in commerce used as a standard of 100 by which the alcoholic strength of a liquor is expressed. The proof of a beverage is roughly twice its percentage; 90 proof means that the article designated contains about 45 per cent of alcohol.

A denatured alcohol is one to which some other substance has been added. This is done to furnish a tax-free article for industry or to render industrial alcohol unfit for drinking. Although a variety of materials are allowed under several formulas, the chief denaturant has been methanol or methyl alcohol, and the product is then often called methylated spirit. Other substances employed are benzene, acetone, diethyl phthalate and zinc phenolsulfonate.

Dehydrated or absolute alcohol is prepared by fractionation in an efficient still, with or without benzene. The last portion of the water may be removed by lime or anhydrous copper sulfate.

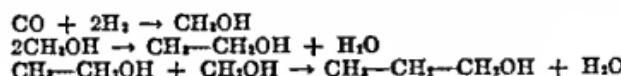
Solid alcohol or "canned heat" is a combination of denatured alcohol with soap or a nitrocellulose, sometimes calcium acetate.

When alcohol, even in dilute aqueous solution (1:2000) is heated with iodine and an alkali, iodoform is produced. Since the latter is insoluble its formation can be observed within limits; if the amount is too small one can usually identify it by the characteristic, very penetrating odor. This reaction is often employed as a test for alcohol, although its value is much lessened by the fact that other substances give an identical product (acetone, acetaldehyde, lactic acid).



Another test for alcohol is the production of esters like the benzoate (see benzoyl chloride).

Normal-propyl alcohol, an official reagent, is a colorless liquid which is miscible with water and has almost the same boiling point. It is a by-product in fermentations and can also be produced synthetically from carbon monoxide and hydrogen in a modification of the method for methyl alcohol.



The control of products is largely one of conditions and of the character of the catalytic agent.

Isopropyl Alcohol N.N.R. has recently come into considerable prominence as a rival of ethyl alcohol for use as a solvent. The chief reason may be found in the ease with which it may be produced from propylene, a product of cracking petroleum, or by reducing acetone. Also it has almost the same boiling point as ethyl alcohol. It is sold as Isopropanol or Petrobol.

Normal-butyl alcohol is one of the chief products from fermentation of cereals (corn) by *Clostridium acetobutylicum* (Weizmann). During the World War I this process was developed to get acetone, at that time very valuable in explosives. Usually butyl alcohol is the chief product while acetone is merely secondary. Another process of manufacture, from acetylene through acetaldehyde and aldol, may become equally important industrially. Butyl alcohol is largely employed as solvent and for the preparation of solvent esters in the making of lacquers. It is also described as an official reagent.

Secondary- and tertiary-butyl alcohols are both available today in large quantities as hydration products of butylenes from cracking of petroleum. They too are used as solvents. The secondary variety contains an asymmetric carbon atom and, hence, exists in levo and dextro forms. Isobutyl alcohol, the fourth isomer, is also employed as reagent.

Commercial amyl alcohol, described as reagent, is a mixture obtained from fusel oil, a by-product in alcoholic fermentation. It is chiefly isobutylcarbinol (about 85 per cent) and active amyl alcohol or sec-butylcarbinol. Another mixture of amyl alcohols has been marketed as "pentosol" obtained from pentanes separated from natural gas. Both of these mixtures are used to prepare solvent esters. Dehydration of amyl alcohol of fermentation gives a substance called amylene, and when this is hydrated again by diluted acid it furnishes tert-amyl alcohol or Amylene Hydrate U.S.P. All eight of the amyl alcohols are known.

Very few of the higher alcohols were of any importance until the advent of efficient cracking processes, but now many of them are available and some have found useful roles in industry. Of the 17 hexyl alcohols most are known, and of the 38 possible heptyl alcohols 13 have been made. Capryl alcohol (octan-2-ol) is described as reagent in the formulary, and 2-ethylhexanol (octyl alcohol) is now an article of commerce. Lauryl or n-dodecyl alcohol, made by reducing coconut oil, is important in industry for producing sodium laurylsulfate.

Cetyl alcohol, $\text{C}_{15}\text{H}_{32}\text{OH}$, found as an ester in spermaceti, can be made

by reduction of palmitic acid. The corresponding product from stearic acid is marketed as stearyl alcohol, $C_{18}H_{37}OH$.

Ceryl alcohol, $C_{26}H_{53}OH$, is contained in beeswax as an ester, and myricyl or melissyl alcohol, $C_{30}H_{61}OH$, is a constituent of carnauba wax.

REVIEW QUESTIONS

1. Write the formulas of a primary, a secondary, and a tertiary alcohol.
2. Write the formulas of 10 heptyl alcohols and name each as a derivative of carbinol and by the Geneva system.
3. State four methods for preparing alcohols.
4. Write equation for preparing from ethanol an alcoholate and an ester of phosphoric acid.
5. How can an alcohol be converted to a halide by phosphorus compounds? Write equation to illustrate.
6. How can alcohols be reduced to hydrocarbon? Illustrate by an equation.
7. Which of the alcohols can be oxidized without disruption of the molecule? Write equation to illustrate.
8. What two classes of compounds can be formed by dehydration of alcohols? Illustrate each.
9. Define proof spirit. What is meant by 110 proof?
10. What is the iodoform test for alcohol? Formulate the equation.
11. How is isopropyl alcohol made? Normal-hutyl alcohol? Secondary-hutyl and tertiary-hutyl alcohols?
12. What are the chief ingredients of fusel oil?
13. What is the natural source of cetyl alcohol? of ceryl alcohol? of myricyl alcohol?
14. Why are lauryl, octyl, and other higher alcohols of more importance than formerly?

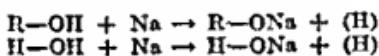
CHAPTER VII

DERIVATIVES OF ALCOHOLS

In this chapter we will consider some compounds which can be obtained directly from alcohols by the reactions previously described, together with compounds which contain halogen or are unsaturated.

ALCOHOLATES

These salts of alcohols were found to be prepared by direct treatment with active metals such as sodium and potassium. The reaction proceeds smoothly and with little of the violence experienced when the same metal reacts with water in an analogous manner.



Some of the alcohols react also with calcium, magnesium, and aluminum, while primary and secondary, but not tertiary, alcohols combine with baryta or lime at elevated temperatures.

The products are usually named, like other salts, by adding the suffix "ate" to the name of the alcohol; for example, sodium ethylate, aluminum n-propylate, and magnesium secondary-butylate. However, many prefer to name the alcoholates as oxides, such as sodium ethoxide, shortened from sodium ethyl oxide. In general in this case the R-O- group is called alkoxide or alkoxy and, specifically, we have methoxy, ethoxy, and butoxy compounds.

The lower alcoholates are colorless, crystalline solids that are soluble in any excess alcohol and can be freed from the latter by evaporation. Water hydrolyzes them completely to alcohol and metal hydroxide. They are frequently used with halides in order to introduce alkoxy groups into organic compounds (Williamson).



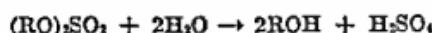
Aluminum ethoxide, prepared by the action of sodium-aluminum alloy on ethyl oxide, is volatile and can be distilled under reduced pressure. It is used as a catalytic and ethylating agent.

ETHERS

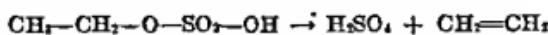
The ethers are compounds of the general formula R-O-R'. They are called simple if R and R' are identical and mixed if these are different. Examples are $\text{CH}_3-\text{O-CH}_3$, and $\text{CH}_3-\text{CH}_2-\text{O-CH}_3$, respectively. The alkyl radicals may be primary and secondary, but tertiary alcohols do not generally form ethers. The compounds are named according to the radicals; thus the two compounds given are dimethyl ether or oxide and ethylmethyl ether or oxide. Occasionally, especially with higher compounds, it is more convenient to name by the Geneva system as alkoxy derivatives. Ethyl-n-propyl ether then becomes 1-ethoxypropane, $\text{CH}_3-\text{CH}_2-\text{O-CH}_2-\text{CH}_3$.

of polybasic acids have little odor, are not volatile, and are readily soluble in water to produce solutions which have an acid reaction and form inorganic salts.

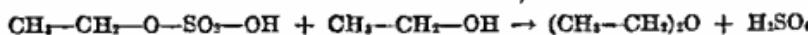
Reactions.—1. All of them are more or less readily hydrolyzed by water or steam, and particularly by boiling with acids or bases.



2. Heated alone the acid esters often decompose to olefines, a reaction which amounts to dehydration of the alcohol.



3. They may also give ethers when heated with alcohols.

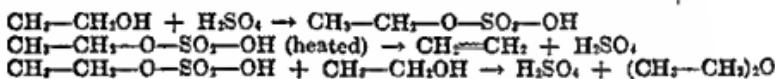


4. Nascent hydrogen converts esters to the hydrocarbon and acid, although the alcohol itself cannot be reduced.—



Dimethyl sulfate is a poisonous, oily liquid which is a very useful aid in the laboratory for methylating, especially of the amines (q. v.).

Diethyl sulfate, which is an oily liquid with a peppermint-like odor, is employed similarly. Ethylsulfuric acid gives a beautiful potassium salt and soluble barium and calcium salts. It is formed as an intermediate in the preparation of ether or ethylene.



Metal alkyl sulfates are much used today as penetrants and wetting agents, the most popular being sodium laurylsulfate.

The nitrates are very unstable and usually explosive. They are easily reduced to hydroxylamine. Nitroglycerin and nitrocellulose are esters of nitric acid with more complex alcohols and will be described later.

Ethyl nitrite, a liquid boiling at 17°, is prepared commercially by the action of nitrous fumes on alcohol or by heating the latter with copper and nitric acid. In the laboratory it is made by action of nitrous acid on alcohol. It is used in medicine as a 4 per cent solution in alcohol under the title of Spirit of Ethyl Nitrite N.F., also known as Spirit of Nitrous Ether or Sweet Spirit of Nitre.

Amyl Nitrite U.S.P., a yellow liquid boiling at 96°, is made from commercial amyl alcohol by similar processes and is, therefore, a mixture. It is used in medicine by inhalation.

Sulfites, borates, arsenates, phosphates, and other esters are also known. The sulfides, which may be considered as derived from the alcohols will be studied later. It should again be emphasized that the halides are esters of the hydrohalogens.

HALOGEN DERIVATIVES

Compounds containing both halogen atoms and the hydroxyl group would have the properties of both, so that no further discussion of these is necessary. A few of them are useful substances.

Chlorobutanol U.S.P. (Acetone-chloroform, Cbloretone), $\text{CCl}_3\text{—COH}(\text{CH}_3)_2$, is made by treating a mixture of chloroform and acetone with solid potassium hydroxide.



It is a local and general anesthetic, hypnotic, and antiseptic.

Brometone N.N.R. is the similar bromine compound, $\text{CBr}_3\text{—COH}(\text{CH}_3)_2$, which is employed in medicine like the bromides.

Iothion N.N.R. (Iopropane), $\text{CH}_2\text{I—CHOH—CH}_2\text{I}$ or 1,3-diiodopropan-2-ol, is used therapeutically for its iodine content, 77 to 80 per cent.

Tribromoethanol U.S.P., $\text{CBr}_3\text{—CH}_2\text{OH}$, is employed somewhat as rectal anesthetic, sometimes under the name Avertin, but by many is considered as dangerous. It is usually administered as the solution with amylene hydrate.

UNSATURATED ALCOHOLS

Several unsaturated alcohols are of some importance. The simplest, vinyl alcohol (etbenol) or $\text{CH}_2=\text{CHOH}$, is unknown; any attempt to make it results in the isomeric compound, $\text{CH}_2=\text{CHO}$ or acetaldehyde. Vinyl halides and other derivatives are stable. It will be recalled the vinyl resins are important commercial products from acetylene.

Allyl alcohol, $\text{CH}_2=\text{CH—CH}_2\text{OH}$, is present in the aqueous product from distillation of wood, along with methyl alcohol and other compounds. It can be made from allyl halides by hydrolysis, but best by heating oxalic acid or formic acid with glycerin. Mild oxidation of allyl alcohol gives glycerin, but stronger action produces acrolein and acrylic acid.

Geraniol, $(\text{CH}_3)_2\text{C=CH—CH}_2\text{—CH}_2\text{—C}(\text{CH}_3)=\text{CH—CH}_2\text{OH}$ or 2,6-dimethyl-octa-2,6-diene-8-ol (or with the first double bond in position 1), and its geometric isomer, nerol, are found commonly in volatile oils, usually as esters. Geraniol occurs in the official oils of coriander, lavender, lemon, nutmeg, orange-flower, and thyme, while nerol gets its name from oil of neroli (orange-flower).

Linalol (linaloöl), $(\text{CH}_3)_2\text{C=CH—CH}_2\text{—CH}_2\text{—C}(\text{CH}_3)\text{OH—CH=CH}_2$, is also an important ingredient of volatile oils. Its acetate is one of the chief components of lavender and coriander oils.

Citronellol, $\text{C}_{10}\text{H}_{20}\text{O}$, of citronella and lemongrass oils, is a primary alcohol having the structure of geraniol but without the second double bond.

Oleyl alcohol, made by reduction of oleic acid, is similar to stearyl alcohol.

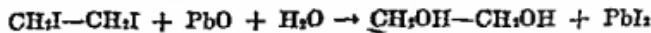
Phytol, found as a constituent of chlorophyll, carotene, and tocopherol, is $\text{IPr—}(\text{CH}_2)_7\text{—CH}(\text{CH}_3)\text{—}(\text{CH}_2)_7\text{—CH}_2\text{OH}$.

Proparaliquid of agreeable odor.

REVIEW QUESTIONS

1. How are the alcohols classified? Write an equation.
- 2.
- 3.
4. What is a simple ether? a mixed ether?
5. State three methods for preparing ethers and write equations to illustrate each.

usually are the dihalides which can be converted with such agents as alkali carbonates, silver oxide, or lead oxide.

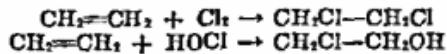


One can also transform the halide first to another ester, such as the diacetate, by heating with metal salts.

2. From olefines by oxidation.- The student will remember that neutral potassium permanganate breaks but one of the two bonds to introduce two hydroxyl groups.



The same result can often be accomplished more satisfactorily by adding chlorine or hypochlorous acid and then hydrolyzing.

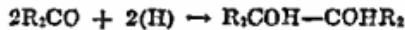


Of course, by these methods there can be obtained only the α, β -type of compounds, in which the two hydroxyl groups are in neighboring carbon atoms.

3. The action of nitrous acid on diamines, perfectly analogous to the process for alcohols. (Chapter XVII.)

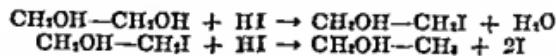
4. Reduction of aldehydes, ketones, or acid derivatives, that already have one hydroxyl group. (Chapters IX, X, XII.)

5. The reduction of ketones gives, along with the normal product of a secondary alcohol, a type of α, β glycols that are called pinacones. (Chapter X.)



Reactions.-1. The glycols form alcoholates, ethers, and esters as do the alcohols, but here we have the possibility of several types, depending on whether one or both hydroxyl groups have been changed and whether both have been affected in the same way. Thus, ethylene glycol furnishes three kinds of ethers, represented by the formulas $\text{CH}_2\text{OR}-\text{CH}_2\text{OH}$, $\text{CH}_2\text{OR}-\text{CH}_2\text{OR}$, and $\text{CH}_2\text{OR}-\text{CH}_2\text{OR}'$. The α, β mono esters of hydrohalogens are very useful in synthesis and easily prepared by the addition of hypohalous acid to unsaturated hydrocarbons, as has already been noted. They contain one hydroxyl group and a halogen atom and are called halohydrins (chlorohydrins, etc.).

2. Like alcohols the glycols are not reducible by nascent hydrogen, but can be reduced in steps by hydrogen iodide, finally to the hydrocarbon. Intermediate compounds that may be isolated are iodohydrins, iodides, diiodides, and alcohols; for example, ethylene glycol may give $\text{CH}_2\text{OH}-\text{CH}_2\text{I}$, $\text{CH}_2\text{I}-\text{CH}_2\text{I}$, $\text{CH}_2-\text{CH}_2\text{I}$, and $\text{CH}_2-\text{CH}_2\text{OH}$. The primary effect on one hydroxyl group is first esterification and then reduction.



3. Oxidation can also take place in two separate directions to give a variety of products, depending upon whether both substituents are affected and to what degree. It will be remembered that a primary alcohol can give dihydroxy and trihydroxy compounds.



A secondary alcohol may yield dihydroxy only, $R_2C(OH)_2$. As example of the possibilities, ethylene glycol may give any or all of the following: $CH_3OH-CH(OH)_2$, $CH_2OH-C(OH)_3$, $CH(OH)_2-CH(OH)_2$, $C(OH)_2-CH(OH)_2$, $C(OH)_3-C(OH)_3$. Which of these can be isolated is dependent on the nature of the agent used and other conditions. There is also the possibility that some oxidizers may disrupt the bond between carbons and thus produce two or more smaller molecules.

4. The reaction of glycols with dehydrating agents is analogous to that of alcohols, but there are two striking differences. As has been noted earlier, dehydration of alcohols may produce ethers or olefines. The glycols can also yield ethers in the same way, but, if the hydroxyl groups are far enough apart, the abstraction of water occurs in a single molecule to furnish an internal oxide, a ring compound.



Such internal ethers are designated as epoxy; the compound formed in this case is 1,4-epoxybutane.

They can also lose water to form olefine derivatives, but when the two hydroxyl groups are in α, β position and sometimes in α, γ , the hydroxy-olefine rearranges to aldehyde or ketone by shifting of hydrogen from oxygen to carbon.



Such a rearrangement is not at all uncommon, unique as it may seem to the beginning student, and we will meet many examples. It is called tautomerism, and the two compounds that are involved are said to be tautomers.

Ethylene glycol is a viscous liquid melting at -11° and boiling at 197° and with a specific gravity of about 1.125. It is miscible with water or

radiator, as preservative, as solvent, and for the manufacture of solvent esters. The dinitrate is an explosive like nitroglycerin and has also been employed like the latter in medicine. The oleate, phthalate, stearate, and other esters are used in industry.

Ethylene oxide, CH_2-CH_2 , might theoretically result from the glycol



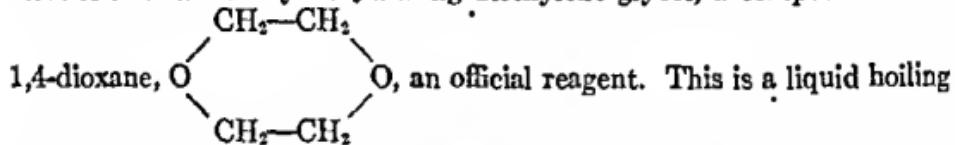
by dehydration. Actually the removal of hydrogen chloride from the chlorohydrin by means of alkalies gives better results. The industrial method for preparing the chlorohydrin is the action of acidified hypochlorites on ethylene, and the product is then distilled with potassium hydroxide to give the oxide, 1,2-epoxyethane. It is an easily liquefied gas that is employed as a fumigant and insecticide; a mixture with carbon dioxide is called Carboxide.

The oxide is readily decomposed and consequently will react with a variety of substances. Many of these reactions give substances useful in commerce, and a large industry has been built around them. Indirectly this expansion was due to the availability of ethylene from cracking petroleum. Water will add slowly to give ethylene glycol, a process that

can be enhanced by small quantities of acid. Concentrated hydrochloric acid adds to yield the chlorohydrin, and nascent hydrogen reacts to produce alcohol. Aldehydes, acid anhydrides, and other compounds also combine, as does also the Grignard reagent.

The most useful reactions of ethylene oxide are in the production of solvents with alcohols and ammonia. Additions of the former can be brought about catalytically to provide the cellosolves, $R-O-CH_2-CH_2OH$. These are named according to the alkyl radical, as methyl cellosolve and butyl cellosolve. They are liquids with boiling points lower than that of ethylene glycol and are excellent solvents for many organic materials, at the same time being miscible with water. Butyl cellosolve boils at 171° . When these compounds are catalytically treated with another molecule of ethylene oxide, there are obtained compounds of the formula $R-O-CH_2-CH_2-O-CH_2-CH_2OH$. These, which are solvents with higher boiling points, are called carbitols; butyl carbitol boils at 223° .

If ethylene glycol is the alcohol that is added to the oxide, a glycol ether is obtained that is called diethylene glycol, $CH_2OH-CH_2-O-CH_2-CH_2OH$. It will be observed that the carbitols are alkyl ethers of it. Diethylene glycol is commonly used in industry as solvent but, since it is poisonous, should not be employed in medicinal preparations for that purpose. Such unjustifiable use by an ignorant manufacturer in 1937 gave rise to the wholesale deaths from "elixir of sulfanilamide." The stearate, oleate, laurate, and other esters are marketed as solvents. Still another solvent is obtained by dehydrating diethylene glycol, a compound called

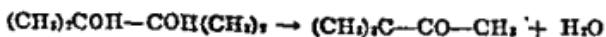


at 102° and hence more volatile than the glycols, cellosolves, carbitols, or ethanolamines. The last named, which are produced by action of ammonia on the oxide, will be discussed later. (Chapter XVII.)

Propylene Glycol N.F., $CH_2-CHOH-CH_2OH$, can be made from propylene by potassium permanganate or hypochlorous acid, or more conveniently by distilling glycerin with potassium hydroxide. It is used as solvent and antifreeze agent. Since it contains an asymmetric carbon atom, there are dextro and levo forms; the racemic mixture that is obtained synthetically can be resolved into these optical isomers. The laurate, oleate, stearate, and other esters are commercial articles.

Trimethylene glycol, $CH_2OH-CH_2-CH_2OH$, is a by-product in the fermentation of glycerin or can be prepared synthetically. The corresponding dibromide is a useful laboratory reagent for the preparation of other compounds.

Pinacone or pinacol, $(CH_3)_2COH-COH(CH_3)_2$, which is produced in the reduction of acetone to isopropyl alcohol, is a liquid that boils at 172° and forms a colorless, crystalline hydrate with water. Heated with dilute acid, it undergoes rearrangement to a ketone, pinacoline, with splitting out of water.

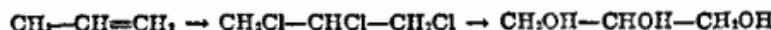


GLYCEROLS

The glycerols or trihydric alcohols have three hydroxyl groups attached to separate carbon atoms. The simplest one is glycerol, the only one of any importance. What has been said about the chemical properties of glycols here also applies, and no entirely new reactions are to be encountered, but only modifications.

Glycerin U.S.P. (Glycerol) is a colorless, heavy viscous, sweet, hygroscopic liquid that boils at about 290° and is miscible with alcohol or water but insoluble in ether. It dissolves bases like calcium hydroxide, probably forming alcoholates. The student is requested to note that the official title is "glycerin" and not "glycerine" as it is sometimes used in industry, and he should be careful to use this official spelling.

Commercially glycerin is prepared by saponification of fats and oils which are all esters of it with certain acids. Some is also made as a by-product in fermentation of sugars to alcohol, and the amount so formed can be increased by modifying the process. The most promising source of glycerin is propylene from the cracking process, and large quantities are now being produced in this way. It is first chlorinated to 1,2,3-trichloropropane and then the latter is hydrolyzed.



Recent figures are designed to show that the cost of glycerin by this method is about half of that by fermentation or the hydrolysis of fats. In the laboratory it can be made by the oxidation of allyl alcohol by means of potassium permanganate.

Reactions.—Being three times an alcohol, glycerin behaves as such in forming alcoholates, ethers, and esters. The products, however, can vary notably according to how many and which hydroxyl groups have been affected. For example, there are two monoacetates, two diacetates, and a triacetate, and if the esterifying acids differed there would be still more.

Oxidation of the glycerin molecule can take place in all three positions, making it a fairly good reducing agent; indeed, the usual method for determining the quantity in given mixtures involves an oxidizing titration, commonly with potassium dichromate. The products of such action would depend upon conditions and the agent used. The primary carbons can each be converted to dihydroxy and trihydroxy groups, while the secondary carbon can form a dihydroxy group; there are 11 possible compounds altogether, and the student should write out for practice the 11 formulas.

Strong dehydrating agents convert glycerin, and also fats, to acrolein, an acrid liquid that will be considered in the next chapter. This is also formed when one subjects either of the two substances to temperatures of about 450° without any agent. The pungent odor of heated fats, so familiar to all of us, is due to the formation of acrolein.

Like the glycols, glycerin can be reduced in steps by hydroiodic acid with or without phosphorus. The possible products of this reaction include triiodopropane, allyl iodide, propylene, and isopropyl iodide. For practice, the student should write equations for forming these and the other possible compounds.

Fermentation of glycerin by yeast gives propionic acid, while that by *Bacillus butylicus* yields n-butyl alcohol, glycol, and other products.

Most of the commercial glycerin is used to make nitroglycerin, but much is employed in the manufacture of inks, as antifreeze agent, in cosmetics, and in many other ways. In addition many of its esters are now available commercially as solvents.

Glyceryl trinitrate (nitroglycerin, glonoin), $\text{CH}_2(\text{ONO}_2)-\text{CH}(\text{ONO}_2)-\text{CH}_2\text{ONO}_2$, is made by the action of nitric acid, using sulfuric acid as dehydrator. It is a colorless oil that boils at about 160° under a pressure of 15 millimeters. Heated quickly or exposed to detonation of mercury fulminate, it explodes violently to form nitrogen, nitrous oxide, carbon dioxide, steam, and other gases. Dynamite is prepared by mixing the liquid with kieselguhr or sawdust, ammonium nitrate, and glyceryl dinitrate to lessen the danger of spontaneous explosion. Smokeless powder is made by mixing with nitrocellulose. Alkalies decompose it to glycerin and nitrates which are not dangerous, and in case some of it or its preparations are spilled on clothes or furniture, one can easily render it harmless by pouring some alkali over the spots. Pharmacists and others working with nitroglycerin are often poisoned by its vapor and should take precautions against inhaling it in too large amounts. Spirit of Glyceryl Trinitrate U.S.P. and Tablets of Glyceryl Trinitrate U.S.P. are used like the nitrites to lower vascular pressure.

Glycerophosphoric acid, $\text{CH}_2\text{OH}-\text{CHOH}-\text{CH}_2\text{OPO}(\text{OH})_2$, is formed by treating glycerin with glacial phosphoric acid. It can also be obtained by hydrolyzing lecithin, a component of egg-yolk, gray matter of brain and nerve, and bile. Salts of the acid used in medicine include Calcium Glycerophosphate N.F., $\text{CaO}_2\text{PO}-\text{O}-\text{CH}_2-\text{CHOH}-\text{CH}_2\text{OH}$; Sodium Glycerophosphate N.F.; Ferric Glycerophosphate N.F.; and Manganese Glycerophosphate N.F.

Glycidic, $\text{CH}_2\text{OH}-\text{CH}(\text{O})-\text{CH}_2$, and epichlorohydrin, $\text{CH}_2\text{Cl}-\text{CH}(\text{O})-\text{CH}_2$,

analogous to ethylene oxide, are well known and useful in synthetic operations.

Fats, which are esters of glycerin with so-called fatty acids, will be considered in a later chapter (XIII).

Erythritol or erythrol, butanetetrol-1,2,3,4, is the analogous tetrabhydroxy compound, $\text{CH}_2\text{OH}-\text{CHOH}-\text{CHOH}-\text{CH}_2\text{OH}$. It is found as ester in many lichens and algae and free in other plants. It is a colorless solid melting at 112° and is soluble in water but sparingly so in alcohol and insoluble in ether. Containing as it does two asymmetric carbon atoms, there are several forms although the commercial article is inactive.

Erythrityl tetranitrate (tetranitrol) is employed in medicine like nitroglycerin and is just as explosive. For administration, it is diluted with inert powder in Tablets of Erythrityl Tetranitrate U.S.P.

Pentanepentol-1,2,3,4,5, $\text{CH}_2\text{OH}-\text{CHOH}-\text{CHOH}-\text{CHOH}-\text{CH}_2\text{OH}$, contains also two asymmetric carbon atoms and can thus exist in a number of forms. The only one that occurs in nature is ribitol, but arabitol can be obtained by the reduction of acacia, and xylitol and adonitol are also known. All of these are related to the pentoses described in Chapter XXII.

The corresponding hexanehexol contains four asymmetric carbons. The best known of the isomers is mannitol or mannite, found in Manna, N.F. and in many other plants, such as larch, sugar cane, agaric, rye-bread, and

viburnum. It is made by reduction of the sugars, levulose or dextrose. Sorbitol, another of the isomers, is employed in the synthesis of ascorbic acid and in the plastic industry. Dulcitol, another of these isomers, as well as mannitol, is used as reagent by the formulary.

REVIEW QUESTIONS

1. Write formulas of the glycols of ethane and propane and name each in two ways.
 2. State four methods for making glycols and write specific equations illustrating.
 3. Write equations to show reduction, oxidation, and dehydration of a glycol.
 4. How is ethylene oxide made from ethylene? Write all equations.
 5. Show by equations the action on ethylene oxide of water, hydrogen chloride, and alcohols
 6. What are the cellosolves and carbitols and how are they made?
 7. Why should not diethylene glycol be used in medicinal preparations?
 8. "
 9. " method.
 10. " without
- disrupting the molecule.
11. What is obtained by heating glycerin or subjecting it to action of a dehydrating agent?
 12. How is nitroglycerin produced? Write the equation. In what forms is it official?
 13. What should be done about spilled spirit of glyceryl trinitrate? Write equation for the resulting action.
 14. What are dynamite and smokeless powder?
 15. Write the formulas of calcium glycerophosphate, erythritol tetranitrate, arabitol, mannitol.

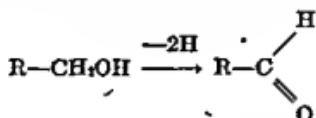
CHAPTER IX

ALDEHYDES

THE oxidation of primary alcohols was found to give compounds with two hydroxyl groups on the same carbon atom.



Such substances, as might be expected, readily and spontaneously lose water to produce the aldehydes, $R-\text{C}\begin{smallmatrix} \text{H} \\ \diagdown \\ \text{O} \end{smallmatrix}$. The ultimate change from the alcohol is represented by the loss of two hydrogen atoms,



Hence, the product is *alcohol dehydrogenatus* which has been shortened to aldehyde. The radical $\text{C}\begin{smallmatrix} \text{H} \\ \diagdown \\ \text{O} \end{smallmatrix}$ is called the aldehyde group and its con-

stituent part $\text{C}=\text{O}$ is referred to as a carbonyl group. It is usual to write the aldehyde group rationally as $-\text{CHO}$ but never $-\text{COH}$.

Nomenclature.—Because there is an aldehyde corresponding to each primary alcohol, the logical name would naturally be derived from that alcohol. Historically, however, the acids that are formed on oxidation were well known and named first, so it is also customary to designate the aldehyde according to its acid. Either one of these two systems has drawbacks just as soon as the radicals get large, and sometimes the aldehyde is named as a derivative of the simplest, formaldehyde $\text{H}-\text{C}\begin{smallmatrix} \text{H} \\ \diagdown \\ \text{O} \end{smallmatrix}$, or of

the second member, acetaldehyde $\text{CH}_3-\text{C}\begin{smallmatrix} \text{H} \\ \diagdown \\ \text{O} \end{smallmatrix}$. Finally, the Geneva system is used where the complexity renders the others cumbersome. Here the aldehyde group is designated by the suffix -al and the aldehyde carbon is included in the chain and is understood as carbon atom number 1.

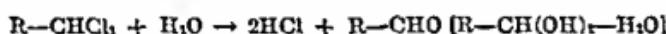
For the first few members of the series we have the names given in the following table.

$\text{H}-\text{CHO}$	methyl aldehyde	formaldehyde	methanal
CH_3-CHO	ethyl aldehyde	acetaldehyde	ethanal
$\text{CH}_3-\text{CH}_2-\text{CHO}$	propyl aldehyde	propionaldehyde	propanal
$\text{CH}_3-\text{CH}_2-\text{CH}_2-\text{CHO}$	n-butyl aldehyde	n-butyraldehyde	butanal
$(\text{CH}_3)_2\text{CH}-\text{CHO}$	isobutyl aldehyde	isobutyraldehyde	2-methylpropanal
$\text{CH}_3-(\text{CH}_2)_2-\text{CHO}$	n-amyl aldehyde	valeraldehyde	pentanal
$(\text{CH}_3)_2\text{CH}-\text{CH}_2-\text{CHO}$	isopropylacet-aldehyde	isovaleraldehyde	3-methylbutanal
$\text{CH}_3-\text{CH}_2-\text{CH}(\text{CH}_3)\text{CHO}$	ethylmethylacet-aldehyde	—	2-methylbutanal
$(\text{CH}_3)_2\text{C}-\text{CHO}$	trimethylacet-aldehyde	—	2,2-dimethylpropanal

Physical Properties.—The aldehydes are neutral, colorless gases to solids with boiling points much lower than those of the corresponding alcohols. The lower members are volatile without decomposition, have a characteristic pungent odor, and are very soluble in water. These properties alter with increased molecular weight; the higher members are odorless, not volatile at ordinary pressure without decomposition, and insoluble in water.

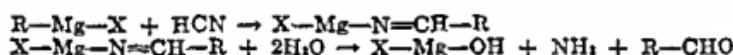
Preparation.—1. As has been noted, they may be made by oxidation of primary alcohols. Because the aldehyde may be oxidized easily to acids, the process must be carefully regulated. Potassium dichromate or manganese dioxide and sulfuric acid are the agents usually employed, but one can even use oxygen itself with carbon, platinum, or other catalytic agent. In industry the alcohol is passed over copper at about 300°, hydrogen being eliminated.

2. The aldehyde may also be obtained by hydrolysis of a dibalide, just as the monohalide gives an alcohol.



Treatment with superheated steam will bring this about sometimes, or the hydrolysis may be accomplished by boiling with water and oxides of silver or lead.

3. The Grignard reagent makes a very convenient method for synthesizing new or well-known aldehydes. The addition of hydrogen cyanide to this reagent gives a compound which can be hydrolyzed to an aldehyde and ammonia.



By selection of RX to make the reagent, any desired aldehyde can thus theoretically be manufactured.

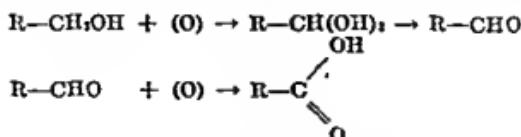
Other methods will be named only and discussion will be postponed until we consider the raw materials.

4. Distillation of metallic salts with metallic formates. (Chapter XII.)

5. Reduction of acid derivatives, such as esters. (Chapter XII.)

Reactions.—The aldehydes are exceedingly active compounds towards a variety of reagents. Most of the changes thus produced are attributable to the carbonyl group, at least one to the aldehyde hydrogen.

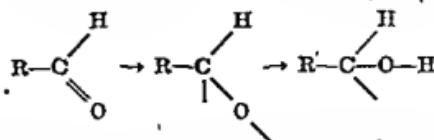
1. As has been stated, they are readily oxidized to acids in a manner similar to the change from alcohol to aldehyde.



Air is able to accomplish this slowly, pure oxygen more rapidly. Stronger agents like chromic or nitric acid can be used, or even such mild ones as the reducible salts of heavy metals. Fehling's solution (alkaline solution of cupric sulfate) or ammoniacal solution of silver nitrate are usually reduced quickly.

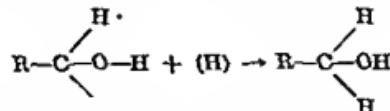
2. As is the case with olefines, the double bond of the aldehyde group represents additive capacity for certain reagents. In this instance the

adding substance must apparently contain hydrogen to make a hydroxyl group.



The rest of the adding molecule goes in at the free bond as indicated.

(a) Nascent hydrogen itself adds in to give a primary alcohol.



This reduction can be performed by sodium amalgam and dilute acid, by zinc dust and acetic acid, by molecular hydrogen and a catalyst at temperatures up to 250° , electrolytically with a mercury cathode, and by other agents. Often as a by-product we find $\text{R}-\text{CHOH}-\text{CHOH}-\text{R}$.

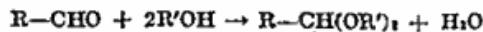
(b) Water will undoubtedly add to form a dubydroxy compound and aqueous solutions probably contain the addition product $\text{R}-\text{CH}(\text{OH})_2$. Attempts to isolate it, however, usually result in loss of water again.

(c) Ammonia often adds in to give aldehyde ammonias, $\text{R}-\text{CHOH}-\text{NH}_2$, which are crystalline and soluble in water. Warmed with water and acid, these dissociate again to the aldehyde, changes which are utilized to isolate and purify the latter.

(d) Hydrogen cyanide gives cyanohydrins, $\text{R}-\text{CHOH}-\text{CN}$, which are useful in making hydroxy-acids.

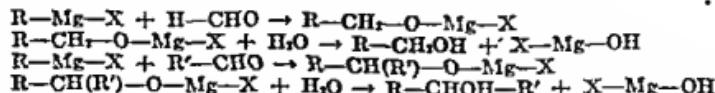
(e) Sodium bisulfite forms crystalline, soluble compounds, $\text{R}-\text{CHOH}-\text{SO}_3\text{Na}$, providing another useful means for separating and purifying aldehydes. The latter can be regenerated by warming the addition compounds with bases or acids. Sulfurous acid will also add in and this gives the basis for the Schiff test for aldehydes. Fuchsin, a purple-red dye, is decolorized by sulfurous acid to make the reagent which then yields this acid to any aldehyde present, liberating the red color.

(f) Often alcohols will combine to give a hemiacetal, $\text{R}-\text{CHOH}-\text{OR}'$, although more often water is split off to give an acetal.



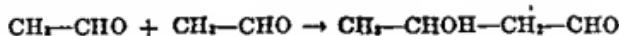
These changes may frequently be encountered during oxidation of a primary alcohol to the aldehyde. The acetals are easily hydrolyzed by warming with acids or more slowly with water.

(g) The Grignard reagent can yield compounds which hydrolyze to secondary alcohols or, if formaldehyde was the starting point, primary alcohols.



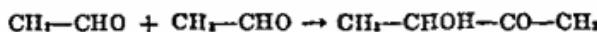
(h) Finally, aldehydes will even add themselves if nothing else is available, as was also the case with olefines. This polymerization can take place theoretically in three different directions best illustrated by using a specific example.

I. The hydrogen in a neighboring carbon atom to the aldehyde group adds to the oxygen for the hydroxyl, and the rest of the second molecule takes up the other bond.

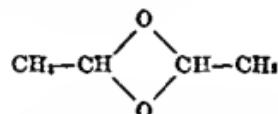


The product in this case, being both alcohol and aldehyde, is called an aldol. Because it is still an aldehyde another molecule of the original compound can be added, and this addition might go indefinitely. The whole process is called aldol condensation, although it is not condensation at all.

II. The aldehyde hydrogen can be the one which forms hydroxyl.



III. Instead of forming a hydroxyl group, the severed bonds of the carbonyl radical could satisfy each other, giving



Under the influence of strong alkalies and warming, resins are formed from the lower members, probably by polymerization of many molecules by the aldol process (I). If diluted alkalies or acids are used, products can be isolated which represent but one or two steps in this process; thus, aldol itself as given above can be formed, and separated, from reaction of two molecules of acetaldehyde. When concentrated acids are used, we get so-called para compounds, probably through the carbonyl groups as in III. This reaction is reversible by heat and reagents.

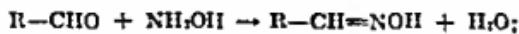
3. Because the aldehyde contains the equivalent of two hydroxyl groups, the reaction with phosphorus pentachloride produces a dichloride.



4. The aldehydes condense with compounds containing the $-\text{NH}_2$ group (primary amines), the products being of most value for identification purposes. In this reaction there may be a preliminary addition as with ammonia,



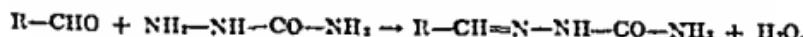
but the ultimate product involves splitting out of water. The three common reagents and their reactions are: hydroxylamine, NH_2OH , which gives oximes,



phenylhydrazine (or other hydrazine derivative), $\text{C}_6\text{H}_5\text{--NH--NH}_2$, which yields phenylhydrazone,

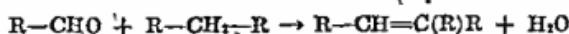


and semicarbazide, $\text{NH}_2\text{--NHNH--CO--NH}_2$, producing semicarbazones,



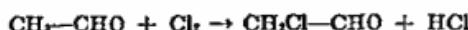
All of these reactions are reversible by hydrolysis.

5. Condensation can also take place with various other compounds. Thus, hydrogen sulfide gives thioaldehydes, $R-\text{CH}=\text{S}$. Even hydrocarbon groups may react to split out water with the carbonyl,

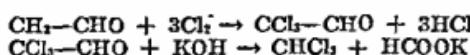


The formation of acetals as described in 2(f) is another illustration of such a condensation.

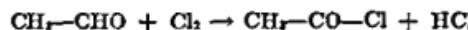
6. Halogens or hypohalites will not react with the aldehyde group except to oxidize, but may substitute halogen for any hydrogen in a neighboring carbon atom.



The halogen may also give the haloform reaction, especially if an alkali is used, as in the hypohalites.



With perfectly dry chlorine, aldehydes are converted to acyl halides (Chapter XII).



Solution of Formaldehyde U.S.P. (Formalin) contains about 37 per cent of HCHO and a small amount of methanol to preserve it from polymerization. The gas, boiling at -21° , is probably produced in the process of photosynthesis from carbon dioxide and water. In the laboratory it is usually prepared by the oxidation of methyl alcohol, either with acidified potassium dichromate or by passing the vapors and air or oxygen over hot copper or silver. Recently much formaldehyde has been made commercially by subjecting water gas to pressure in the presence of certain metallic oxides as catalysts.

Formaldehyde is usually employed in the form of the aqueous solution to harden tissues as anatomical specimens and to act as antiseptic and preservative. It is also used in industry to make artificial resins and plastics, such as with phenol to make Bakelite. Concentrated sulfuric acid converts it to paraformaldehyde, from which the aldehyde can be regenerated by heat. Alkalies convert formaldehyde to methanol and formates (Cannizzaro) or, if dilute, into a mixture of sugars by aldol polymerization. No resinification can be obtained as with other aldehydes. Methyl alcohol will condense with it to form Methylal, $\text{CH}_2(\text{OCH}_3)_2$, which has been used as a hypnotic. It is notable that ammonia will not add to formaldehyde as with other members of the series, but condenses with it to produce the official Metbenamine.

Acetaldehyde is a liquid boiling at 20° to 21° and is typical of the lower members. It can be prepared by any of the general methods, but in commerce can also be produced by the catalytic hydration of acetylene



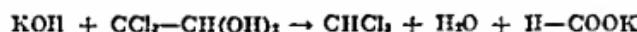
a process which promises to be of great value.

Paraldehyde U.S.P. (CH_3-CHO)₂ can be produced from acetaldehyde by contact with sulfuric acid. It is a liquid which boils at 124° , decomposes to acetaldehyde on heating with dilute acids, and has physiological actions

very similar to those of alcohol. A solid polymer, metaldehyde, is formed with sulfuric acid at low temperature.

Other aldehydes, with 8 to 10 carbon atoms, are now easily obtained from petroleum and at small cost.

Chloral Hydrate U.S.P. Chloral, $\text{CCl}_3\text{—CHO}$, is produced by action of chlorine on alcohol, during which process chloral alcoholate, $\text{CCl}_3\text{—CH(OH)—O—CH}_2\text{—CH}_3$, and trichloroacetal, $\text{CCl}_3\text{—CH(O—CH}_2\text{—CH}_3)_2$, are intermediate. The chlorine here acts as chlorinating and oxidizing agent. Anhydrous chloral, a liquid boiling at 98° , has all of the typical reactions of aldehydes. It will unite with water to form chloral hydrate, $\text{CCl}_3\text{—CH(OH)}_2$, a stable crystalline compound which has none of the properties of aldehydes, although it can be dehydrated again to chloral. Alkalies or ammonia decompose it to chloroform and formates.



Betyl Chloral Hydrate N.N.R., $\text{CH}_3\text{—CHCl—CCl}_2\text{—CH(OH)}_2$, is a crystalline substance with similar properties.

Acrolein, $\text{CH}_2=\text{CH—CHO}$, which is also called acrylic aldehyde and propenal, can be obtained by oxidation of allyl alcohol. It is produced whenever a fat or glycerin is heated alone or with a dehydrating agent. The chief gases arising from heated fats consist largely of acrolein.

Crotonic aldehyde, $\text{CH}_3\text{—CH=CH—CHO}$, can be obtained by distilling indol or by dehydrating it in other ways.



It is used commercially in the manufacture of rubber and plastics, as insecticide, and in other ways.

Citral, the chief odorous component of lemon oil and quite widely spread in volatile oils generally, is the aldehyde corresponding to geraniol and can be obtained from the latter by oxidation.

Glycollic aldehyde, $\text{CH}_2\text{OH—CHO}$, is a crystalline solid that is very soluble and very sweet. It is made from ethylene glycol by oxidation with hydrogen peroxide.

Glyceraldehyde, $\text{CH}_2\text{OH—CHOH—CHO}$, is theoretically a sugar and can readily be converted to acrose, a mixture of true sugars by aldol condensation. It contains an asymmetric carbon atom.

Aldol, $\text{CH}_2\text{—CH(OH)—CH}_2\text{—CHO}$, is formed by treating acetaldehyde with dilute alkalies, a typical aldol condensation. This compound also has an asymmetric carbon.

Glyoxal, CHO—CHO , is a greenish gas that easily polymerizes. Dimethylglyoxime, $\text{CH}_3\text{—C(=NOH)—C(=NOH)—CH}_3$, described as pharmaceutical reagent, is the oxime of diacetyl (Chapter X).

REVIEW QUESTIONS

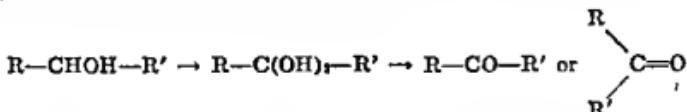
1. Write general formulas for an aldehyde, the aldehyde group, and the carbonyl group.
2. In what four ways are aldehydes named? Formulate all of those having up to 5 carbon atoms, including the ones having a double bond, and name each in the three ways.
3. Write equations for the formation of aldehydes by oxidation of primary alcohols, by hydrolysis of d.l. aldehydes, and through the Grignard reaction.
4. State two other ways for preparing.

- 5. Write equations for reduction and for oxidation of some particular aldehyde.
- 6. Illustrate by equations the addition of water, alcohol, hydrogen cyanide, sodium bisulfite, sulfuric acid, ammonia, and the Grignard reagent.
- 7. What is aldol condensation? How is it brought about? Illustrate using propyl aldehyde.
- 8. What is the product of boiling an aldehyde with alkali? of treating it with concentrated acid?
- 9. Write equations to show action of phosphorus pentachloride, of hydroxylamine, of phenylhydrazine, and of semicarbazide. What is the product in each case called?
- 10. In what form is formaldehyde official?
- 11. What are formalin, bakelite, paraformaldehyde, an acetal, a hemiacetal?
- 12. What is Paraldehyde U.S.P. and how is it made?
- 13. Why does Chloral Hydrate U.S.P. not give reactions of aldehydes? What happens to it on warming with alkalies?
- 14. Write the formulas of butyl chloral hydrate, acrolein, crotonic aldehyde, citral, aldol, glyoxal, glycollic aldehyde, glyceric aldehyde.

CHAPTER X

KETONES

As has already been noted, the oxidation of secondary alcohols gives rise to dihydroxy compounds with the groups on a secondary carbon atom. Just as the corresponding primary dihydroxide lost water spontaneously, so also do these to form ketones.



Like the aldehydes, these contain the carbonyl group and may be regarded as derived by substituting the hydrogen of the aldehyde group by alkyl. If the two radicals in this ketone are identical the compound is called simple, but if they are different we refer to it as a mixed ketone.

Nomenclature.—The ketones are named according to the two radicals as alkyl alkyl ketones; as a derivative of the simplest in the series, dimethyl ketone or acetone; or by the Geneva system using the suffix -one for the carbonyl group. The names in each way for a few compounds are given in the following table.

$\text{CH}_3-\text{CO}-\text{CH}_3$	acetone	dimethyl ketone	propanone
$\text{CH}_3-\text{CO}-\text{CH}_2-\text{CH}_3$	methylacetone	ethyl methyl ketone	butanone
$\text{CH}_3-\text{CH}_2-\text{CO}-\text{CH}_2-\text{CH}_3$	sym-dimethylacetone	diethyl ketone	pentan-3-one
$(\text{CH}_3)_2\text{CH}-\text{CO}-\text{CH}_3$	unsym-dimethylacetone	isopropyl methyl ketone	2-methylbutanone

If hydroxyl or ketone groups are substituents in an aldehyde, the last is given preference as suffix, and the first two become the prefixes hydroxy- and keto-, instead of the usual suffixes -ol and -one respectively. Upon these rules $(\text{CH}_3)_2\text{CH}-\text{CH}_2-\text{CO}-\text{CH}_2\text{OH}$ is 4-methyl-1-hydroxypentan-2-one and $\text{CH}_3-\text{CO}-\text{CHOH}-\text{CH}(\text{CH}_3)-\text{CHO}$ is 2-methyl-3-hydroxy-4-ketopentanal. It is also well to emphasize again that the aldehyde group can only be at the end of a chain and that it is understood as 1 position. Thus, butanal can have only one formula and stands for butanal-1, $\text{CH}_3-\text{CH}_2-\text{CH}_2-\text{CHO}$. Again, $(\text{CH}_3)_2\text{CH}-\text{CH}_2-\text{CHO}$ is 3-methylbutanal and not 2-methylbutanal-4.

The lower ketones are neutral liquids that are soluble in water or alcohol and possess a characteristic odor. As the molecular weight increases the odor and solubility become less and the volatility decreases.

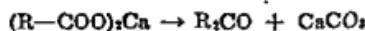
Preparation.—The methods usually used are similar to those already listed for the aldehydes.

1. Oxidation of secondary alcohols proceeds readily using any agent that is not strong enough to disrupt the molecule; potassium dichromate in acid solution is satisfactory. On a commercial scale this can be done, as with primary alcohols, by passing vapors of the alcohol over copper at high temperature.

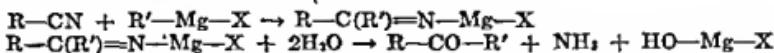
2. The hydrolysis of an appropriate dihalide can often be accomplished by boiling with water, but usually better with an aqueous base.



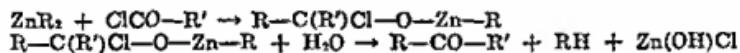
3. The distillation of salts of calcium or barium is often used for the simple ketones. (Chapter XII.)



4. Addition of the Grignard reagent to cyanides or amides and subsequent hydrolysis is similar to the production of aldehydes using hydrogen cyanide. (Chapter XX.)

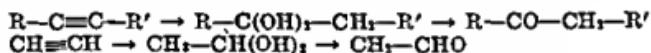


An older method involving similar principles consisted in treating metal alkides, such as ZnR_2 , with acyl chlorides (Chapter XII).



5. The ketones may be prepared from derivatives of acetoacetic acid by warming with dilute acids or alkalies. (Chapter XIV.)

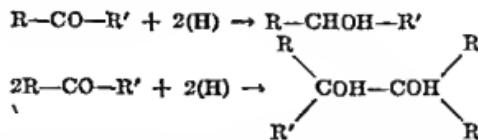
6. The catalytic hydration of acetylenes yields ketones, although acetylene itself gives acetaldehyde; an intermediate product in each case is a dihydroxy compound.



The hydration can be brought about at lower temperatures in the presence of sulfuric acid or solutions of mercuric salts.

Reactions.—Those properties of the aldehydes which are attributable to the carbonyl group are also found typical of ketones, although with some modification, but the oxidizable hydrogen is lacking in the ketones.

1. Nascent hydrogen reduces them to secondary alcohols, but at the same time there is obtained as a by-product a pinacone or pinacol, previously discussed under the glycols.



Ordinary hydrogen with a catalyst will suffice for the reduction below 200° , but above this temperature the equation is reversed. While the pinacol is usually small in amount, its quantity can be increased by using magnesium amalgam for the reduction.

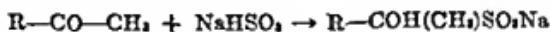
2. Oxidation of ketones is not readily accomplished because, unlike the aldehydes, the carbonyl group has no hydrogen attached to it. Hence, they give no reduction of mild agents such as ammoniacal silver nitrate. The more powerful agents generally split the ketone into two or more molecules, mostly at the union with the carbonyl group in such a way that the latter goes with the smaller residue. Thus, $CH_3-CH_2-CH_2-CO-CH_3$ splits so that the two pieces are mostly $CH_3-CH_2-CH_2-$ and $-CO-CH_3$. In any event, we can conclude that the ketones are never

strong reducing agents like the aldehydes. For a recapitulation of the types of oxidation in organic chemistry and to learn what happens to the two pieces above, see the next chapter.

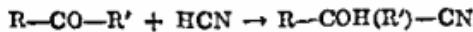
3. As with aldehydes, phosphorus pentachloride acts upon the carbonyl group to replace the oxygen (equivalent to two hydroxyls) by two chlorine atoms.



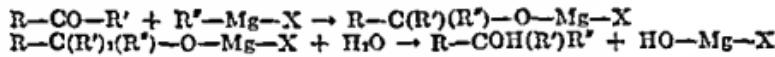
4. Addition often takes place at the double union of oxygen just as it did with aldehydes although not to the same degree. Alkali bisulfites give crystalline compounds with alkyl methyl ketones but not with the alkyl alkyl variety.



Hydrogen cyanide also adds in to form cyanohydrins.



Heating the bisulfite compound with metallic cyanides will also yield the cyanohydrins. The Grignard reagent combines with ketones to form products that hydrolyze to tertiary alcohols.



Ammonia will add at extremely low temperatures but ordinarily forms various condensation products, such as diacetonamine, $(\text{CH}_3)_2\text{C}(\text{NH}_3)\text{-CH}_2\text{-CO-CH}_3$.

5. Polymerization of ketones does not occur, although under the influence of dilute alkalies two molecules of acetone will add together to form diacetone alcohol, $(\text{CH}_3)_2\text{COH-CH}_2\text{-CO-CH}_3$. In the presence of acids or zinc chloride it will condense to form mesityl oxide, $(\text{CH}_3)_2\text{C=CH-CO-CH}_3$, or a similar product.

6. Compounds containing the $-\text{NH}_2$ group react with ketones as with aldehydes. Hydroxylamine gives ketoximes, $R_2\text{C=NOH}$; semicarbazide yields semicarbazones, $R_2\text{C=N-NH-CO-NH}_2$; while phenylhydrazine gives phenylhydrazone, $R_2\text{C=N-NH-C}_6\text{H}_5$. These compounds are often crystalline and of great aid in identification. Hydrogen sulfide will also condense to produce thioketones, $R_2\text{CS}$.

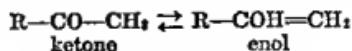
7. Halogens have no effect upon the carbonyl group but substitute in the hydrocarbon radical. Hypohalites or halogens with alkalies react with methyl alkyl ketones to give the haloform reaction, a combined oxidation and halogenation.



This haloform formation is a convenient means for preparing iodoform and chloroform and also to make the compounds $R\text{-COOK}$.

Tautomerism.—In many ketones, and to a lesser extent in aldehydes, there is undoubtedly present a certain amount of an isomer formed by shifting of a hydrogen atom. While in the ketones under consideration the amount of this isomer is very minute, yet in some, such as acetoacetic ester to be described later, this occurrence of altered molecules is very important. The phenomenon can only be explained by the shifting of one

hydrogen atom neighboring to the carbonyl group to give an enol in place of a ketone.



As we have learned previously, such a wandering of atoms or radicals to form new structures is called tautomerism, and the isomers are referred to as tautomers. The enol compound is, therefore, a tautomer of the ketone. Since the enol possesses its hydroxyl group, the hydrogen can often be substituted by metals. It should be carefully noted that the reaction is a reversible one and the equilibrium can be altered by causing a chemical change in either isomer. In many cases, such as we have noted previously, the tautomerization is not reversible.

Acetone U.S.P. (Propanone, Dimethyl Ketone) is a colorless, mobile liquid with a characteristic odor, boiling at 56° and having a specific gravity of about 0.81. It is miscible with alcohol, ether, or water, but can be salted out from an aqueous solution.

It was formerly made entirely by wood distillation, but during the war of 1914-1918 the large quantities needed for explosives were obtained by fermentation of corn and other grains by means of a special bacillus; n-butyl alcohol and carbon dioxide were by-products. After the need for acetone had decreased, butyl alcohol became increasingly important for preparing various esters and soon was the major product. Acetone is also made by catalytic oxidation of isopropyl alcohol obtained from the cracking of petroleum. The former method of heating calcium acetate has more recently been modified by passing vapors of acetic acid over manganese oxide at 300° .



Acetone is employed in tanks of acetylene to prevent explosions and as a general solvent. It is the basis for the synthetic manufacture of sulfonmethane, sulfonethylmethane, smokeless powder, celluloid, chloro-hutanol, iodoform, chloroform, and many other substances.

Ethyl methyl ketone, boiling at 80° , is soluble in about four times its volume of water. It is present in the crude product obtained by the distillation of wood. Amyl methyl ketone, ethyl amyl ketone, and methyl nonyl ketone are found in oil of rue and several other volatile oils.

Monochromoacetone, $\text{CH}_2\text{Br}-\text{CO}-\text{CH}_3$, was developed many years ago as a tear gas or lachrymator. Monochloroacetone and dichloroacetone have similar properties.

Methylheptenone, $\text{CH}_3-\text{CO}-\text{CH}_2-\text{CH}_2-\text{CH}=\text{C}(\text{CH}_3)_2$, probably a degradation product of the terpene derivatives, is a very common constituent of volatile oils.

Pinacoline, $(\text{CH}_3)_3\text{C}-\text{CO}-\text{CH}_3$, and its alkyl derivatives are formed from pinacols by heating with dilute acids. By such means one can proceed from a ketone by reduction to a more complex one containing a tertiary alkyl group.

Ketene, $\text{CH}_2=\text{CO}$, can be prepared by passing acetone, acetic anhydride, or acetic acid over a heated platinum wire, or by the action of sodium or zinc dust on chromoacetyl bromide.



Its alkyl substitution products are obtained in a similar manner. All of them are unstable and very reactive and are sometimes useful in synthesis because of these reactions. Ketene itself is a colorless, poisonous gas boiling at -56° .

Many hydroxyketones, keto-aldehydes, and diketones have been prepared, some of them at present available in commerce. Acetol, $\text{CH}_3\text{—CO—CH}_2\text{OH}$, can be obtained by oxidizing propylene glycol, as can also pyruvic aldehyde, $\text{CH}_3\text{—CO—CHO}$, which has been found in volatile oils. Acetoin, $\text{CH}_3\text{—CHOH—CO—CH}_3$, a product of fermentation and on the market, is a liquid boiling at about 140° . Diacetone, $\text{CH}_3\text{—CO—CH}_2\text{—COH—(CH}_3)_2$, and dihydroxyacetone, $\text{CH}_2\text{OH—CO—CH}_2\text{OH}$, are other common hydroxyketones. Among the diketones may be mentioned acetylacetone, $\text{CH}_3\text{—CO—CH}_2\text{—CO—CH}_3$, and acetonylacetone, $\text{CH}_3\text{—CO—CH}_2\text{—CH}_3\text{—CO—CH}_3$, which are marketed products. The most important, however, is diacetyl, $\text{CH}_3\text{—CO—CO—CH}_3$, a yellow liquid with a sharp odor. It is very common in nature and is a product in distilling many volatile oils. Its oxime has already been mentioned. (Chapter IX.)

REVIEW QUESTIONS

1. Write a general formula for the ketones.
2. Select formulas for any three ketones having each a total of 7 carbon atoms and name each in three ways.
3. Write formulas for acetone, ethyl methyl ketone, propanone, butanone, pentan-3-one, and 3-methyl-2-penten-4-one.
4. How are the ketones prepared from secondary alcohols? from dihalides? Write equations to illustrate.
5. How are they made from salts? with the Grignard reagent? from derivatives of acetoneacetic acid? from homologues of acetylene? Write equations for each reaction.
6. What is the chief product of reduction of a ketone? What other substance is also obtained? Write equations for both reactions.
7. What happens to a ketone upon oxidation? Why are the ketones poor reducing agents?
8. Write equations showing the action of sodium bisulfite, of hydrogen cyanide, of phosphorus pentachloride, of the Grignard reagent, of halogen and hypohalites, of hydroxylamine, of phenyllhydrazine, and of semicarbazide.
9. State four commercial methods for producing acetone.
10. Name three other ketones found in volatile oils.
11. For what is monohromoacetone used?
12. How are the pinacolines made from ketones? Write equations to illustrate the changes.
13. Write equation to show the preparation of ketene from acetic acid.
14. Define tautomerism and tautomer. Show by an equation the change of a ketone to enol.
15. Write formulas for diacetyl, acetol, acetoin, acetonylacetone.

CHAPTER XI

ACIDS

THE substitution of hydroxyls for all three hydrogen atoms of a methyl group gives rise to ortho acids, $R-C(OH)_3$. None of these is known in the free state, although esters of some of them are stable compounds. The

usual acid is formed from the ortho by loss of water, giving $R-C\begin{array}{c} O \\ \diagdown \\ OH \end{array}$

or as commonly written $R-COOH$. This is really the meta acid but, since the ortho is not important, is usually referred to merely as an acid. The characteristic group of organic acids is $-COOH$, called the carboxyl group from carbonyl and hydroxyl. The hydrogen of this carboxyl is replaceable by metals when the acid is treated with bases like inorganic oxides and hydroxides, just as is the hydrogen of inorganic acids.

The series of compounds formed by substituting the carboxyl group for one hydrogen in members of the paraffin series has the general formula $C_nH_{n+1}COOH$. This is empirically equivalent to $C_{n+1}H_{2(n+1)}O_2$ or simply $C_nH_nO_2$. From the first and second members it is called the formic or acetic acid series, also the saturated monobasic acids or the fatty acid series. The common members were known and studied very early in the development of organic chemistry, and the names given to them then were ultimately transferred as roots to the paraffins and other derivatives. Thus, propane, propyl alcohol, and propionic aldehyde were named from propionic acid, meaning first fat, because it can be salted out as an oil from aqueous solution. In a similar manner, butane, butyl alcohol, and butyric aldehyde received their names from butyric acid found in butter.

Nomenclature.—The members of this series were originally assigned specific names to indicate source, and the most commonly occurring ones are still so designated. As the number of known compounds greatly increased and many were made synthetically, the newer ones were described as substitution products of acetic acid. The inadequacies of both systems were soon apparent and led to the adoption of Geneva names, in which the ending -oic replaces the final -e of the hydrocarbon. The carbon of the carboxyl group is assumed to be number 1 and not designated; other substituents that are usually indicated by suffixes are then given prefixes, for the aldehyde group oxo-.

In the table below are given all of the members through five carbon atoms, with names in the three ways.

$H-COOH$	formic	methanoic
CH_3-COOH	acetic	ethanoic
CH_3-CH_2-COOH	propionic	propanoic
$CH_3-(CH_2)-COOH$	butyric	butanoic
$(CH_3)_2CH-COOH$	isobutyric	2-methylpropanoic
$CH_3-(CH_2)_2-COOH$	valeric	pentanoic
$(CH_3)_2CH-CH_2-COOH$	isovaleric	3-methylbutanoic
$CH_3-CH_2-CH(CH_3)-COOH$		2-methylbutanoic
$(CH_3)_3C-COOH$		2,2-dimethylpropanoic

The higher normal acids that are commonly encountered are shown in the following table, with a number indicating total carbon atoms and the Geneva names.

6	caproic	goat milk	hexanoic
7	oenanthic	Oenanthe	heptanoic
8	caprylic	goat milk	octanoic
9	pelargonic	Pelargonium	nonanoic
10	capric	goat milk	decanoic
11			undecanoic
12	lauric	Laurus	dodecanoic
14	myristic	Myristica	tetradecanoic
16	palmitic	palm	hexadecanoic
18	stearic	stearin	octadecanoic
20	arachidic	Arachis (peanut)	eicosanoic
22	behenic	ben oil	docosanoic
24	lignoceric	lignin	tetracosanoic
26	cerotic	wax	hexacosanoic
30	melissic	Melissa	triacontanoic

It is often the practice in the higher members to omit that portion of the Geneva names which gives the ending of the hydrocarbon. Thus, dodecanoic becomes dodecoic, and octanoic becomes octoic acid. Also, sometimes -anoic is changed to -ylic, as deylic for decanoic.

The International Union of Chemistry has approved also another system for naming acids, in which the carboxyl group is viewed as a substituting one. In more complicated compounds this may be designated by the prefix carboxy-, with appropriate number, but in the simple acids of the acetic series it is denoted by the suffix -carboxylic acid. Thus, $\text{CH}_3\text{---COOH}$ is carboxymethane or methanecarboxylic acid.

When the carboxyl radical is linked to a primary carbon atom, it is called a primary acid, secondary and tertiary acids being defined in a corresponding way. Representatives of the three types would have respectively the formulas $\text{R---CH}_2\text{---COOH}$, $\text{R}_2\text{CH---COOH}$, and $\text{R}_3\text{C---COOH}$.

Those acids of the series that contain up to 5 atoms of carbon are frequently found in natural materials, mostly in volatile oils and in the distillation products of animal and vegetable matter. Butyric and most of the higher ones with an even number of carbon atoms up to 30 are found combined in fats and waxes and can be obtained from these by hydrolysis. Those with an odd number of carbon atoms are not generally found in nature.

The lower members are colorless liquids that are miscible with water, have strong characteristic odors, and can be distilled with steam. As the molecular weight increases the solubility, volatility, and odor become less; the higher ones are insoluble, unctuous, white solids without odor or taste. Formic acid is fairly strong, but the others are much weaker, and in general members of this series are practically non-ionized. They are all soluble in alcohol, chloroform, ether, and other organic solvents.

Preparation.—1. As we have seen, they can be made by oxidation of primary alcohols and aldehydes. For this purpose chromic acid or acidified potassium permanganate is usually the agent, and there is little danger of carrying the process too far. Alcohols and aldehydes with high molecular weight may require more strenuous action.

2. Several derivatives of these acids can be converted to the latter by hydrolytic means. Water itself often accomplishes this purpose, but the usual procedure is to boil with dilute mineral acids or bases. Of course, if

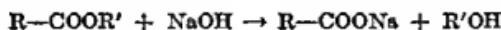
bases are employed the acid is obtained in the form of a salt. In order to free the compound from this salt, we can add a mineral acid and extract or distil.

Cyanides or nitriles, which are conveniently prepared from the halides, are readily converted by boiling with a base.



During this operation amides, $\text{R}-\text{CONH}_2$, are intermediate products, so that these amides can also be employed for the hydrolysis. (Chapters XVII and XVIII.)

Esters of the acids are similarly converted by boiling with bases to an alcohol and the salt, and the latter may then be treated with mineral acids as before. (Chapter XII.)



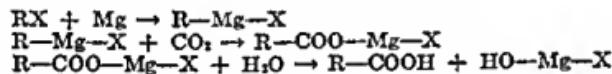
Acid halides and anhydrides can be used also, and in these cases boiling with water is often sufficient. Tribhalides, in which all of the halogen atoms are connected to the same carbon atom, are converted to acids by treatment with moist silver oxide or with dilute aqueous bases.



Thus, chloroform can be hydrolyzed to the first member of this series.



3. Use of the Grignard reagent is a very convenient method for producing acids from monohalides. In this case carbon dioxide is bubbled into the reagent for several hours, and the product is then hydrolyzed by addition of dilute acid or ammonium chloride.

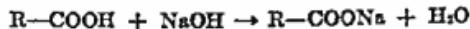


The treatment of metal alkides with carbonyl chloride gives a similar production of acids. (Chapter XX.)

4. In synthetic processes the acids are frequently made from aceto-acetic ester or from malonic ester, both of which will be described later. (Chapters XIV and XV.)

Several other methods are of much less importance: 5. Reaction of alcoholates and carbon monoxide; 6. Reduction of unsaturated acids; 7. Fusion of unsaturated acids with potassium hydroxide; 8. Reduction of hydroxy-acids by means of hydrogen iodide; 9. Heating of dibasic acids; 10. Direct oxidation of hydrocarbons in the presence of a catalytic agent, a method that has more recently become a commercial one.

Reactions.—1. The hydrogen of the carboxyl group is replaceable by a metal, often through direct liberation of hydrogen by the metal itself, but mostly through neutralization by means of the carbonate, hydroxide, or oxide.



As has previously been pointed out, the members of this series are comparatively weak acids, but if hydrogens in the alkyl groups are replaced by halogens, the strength is markedly increased; indeed, some of the halogen acids are almost as highly ionized as hydrochloric acid.

2. Alcohols react to yield esters, just as they do with mineral acids to give inorganic esters.



The reaction proceeds very slowly and is never complete unless one uses a dehydrating or other agent such as zinc chloride, sulfuric acid, or hydrochloric acid. Any substituent in the alpha position retards the esterification, a good example of what is known as "steric hindrance." The weaker the acid, the less easily is it esterified, although the character of the alcohol is also a factor. Primary alcohols react most readily, while tertiary ones can be esterified only with difficulty.

3. Strong dehydrating agents withdraw water to give acid anhydrides.



This is performed industrially with sulfur chloride or phosphorus oxychloride, but in the laboratory we may use also carbonyl chloride, phosphorus pentoxide, or some other strong agent.

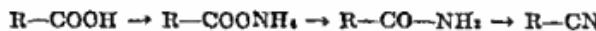
4. Because acids contain the equivalent of three hydroxyl groups, just as aldehydes and ketones have two and alcohols one, we might expect that phosphorus pentachloride would replace them with three chlorine atoms. Actually, however, only one is easily converted, giving an acid chloride.



In place of the phosphorus compound one can use other chlorides, such as sulfuryl, thionyl, or phosphoryl. Acid bromides and iodides are also known but are relatively unimportant.

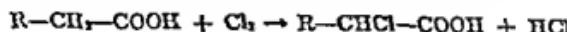
The radical $\text{R}-\text{CO}-$ is called "acyl" in general, and the name of one derived from an individual acid is formed by dropping the ending -ic and adding -yl. Thus, we have acetyl chloride from acetic acid and propionyl chloride from propionic acid, as well as acyl chlorides in general. It should be observed that the acid anhydrides are acyl oxides. Whenever the acyl radical is used in combination names, it is customary to substitute the ending -o for -yl or to omit it entirely. Illustrative names are acetoacetic acid and acetanilid.

5. Ammonia neutralizes the acid to produce an ammonium salt, but when the latter is heated it dehydrates to an amide and then to a cyanide.



It will be noted that this method is the reverse of that used to make the acids by hydration of amides or cyanides. Both reactions will be taken up in greater detail in Chapters XVII and XVIII.

6. While halogenation of hydrocarbons produces a mixture of substitution products and the process can hardly be controlled, the halogenation of acids proceeds smoothly and can be regulated without difficulty. With some of the higher acids there may be encountered some resistance that can be obviated by using the acid chloride or by employing phosphorus along with the halogen. The process involves substitution of halogen for hydrogen in the alpha position to the carboxyl, and in the absence of such alpha hydrogen no action takes place at all.



A second atom of halogen can be made to enter the alpha position, but this requires more strenuous action. Acetic acid, which is the only one having a third alpha hydrogen, can form trichloroacetic acid.

7. Reduction of acids is usually not practicable, but they can first be converted to simple derivatives such as esters or chlorides, and these undergo reduction readily to primary alcohols. Of course aldehydes are intermediate but cannot be isolated. More recently it has been found possible to reduce acids at high temperatures and pressures by means of a catalytic agent to either alcohols or hydrocarbons, depending on the agent used.

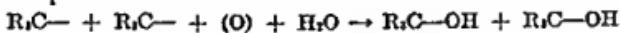
8. Oxidation of acids normally results in splitting the molecule, just as we found was the case with ketones. In order to make this perfectly clear, it will be necessary to consider in detail the processes of oxidation in organic chemistry.

In the ordinary laboratory methods there are just two ways by which substances are oxidized. We may ignore the direct action on hydrocarbon radicals for the present because, although it will be encountered later and is sometimes used commercially, such action is a special case and is really a modification of one that we are now considering. For the first condition (a) we must have hydrogen attached to an already oxygenated carbon,

represented diagrammatically by R_2C  . Answering this requirement

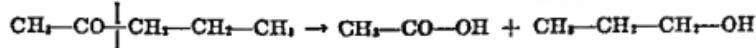
are primary and secondary alcohols and aldehydes, all of which are easily oxidized; the hydrogen in each case is converted to a hydroxyl group merely by the addition of an atom of oxygen.

In the second condition (b) a bond between carbon atoms is first severed and hydroxyl groups (from oxygen and water) are introduced at the free bonds so formed.

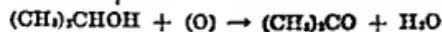
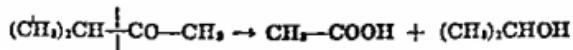


Should either of the two compounds that are produced conform to condition (a) (*i. e.*, if any of the R's is hydrogen), it will naturally oxidize further because the intensity of action necessary to split a bond is usually greater than that needed in (a).

A few examples may serve to make the conditions clearer and will point out the applications to acids. Ketones were found to split at the carbonyl group, usually so that the latter goes with the smaller alkyl. Methyl propyl ketone would thus give primarily acetic acid and propyl alcohol.



But the last will go further by (a) to an acid, and the final products are acetic acid and propionic acid. As a contrast, methyl isopropyl ketone would give acetic acid and isopropyl alcohol, which immediately is transformed to acetone.



Again, ethyl tert-butyl ketone gives primarily propionic acid and tertiary butyl alcohol, and these are the final products. Of course, if any of the substances that are formed should split again, we might get still smaller molecules. If one carbon atom is split off it always becomes carbonic acid, so that the ultimate product of continual oxidation from any compound is simply carbon dioxide with water. Thus, acetic first yields carbonic acid and methyl alcohol, which oxidizes through formaldehyde and formic acid to carbon dioxide. The student is urged to try severing the molecules of the fatty acids at various places and determine the compounds formed without further splitting. Usually a mixture of the possible products results. Unsaturated compounds are severed at the multiple bonds and each free bond set free takes up hydroxyl.

Formic Acid N.F. is an aqueous solution containing about 25 per cent of methanoic acid, H—COOH. The name is derived from the Latin *Formica*, meaning ant, because it was originally obtained by distillation of red ants. It is also present in caterpillars, tamarinds, perspiration, meat juices, and a large variety of other materials. Anhydrous formic acid is a liquid with an acetous odor, boiling at 101° and melting at 8° to 9°. It is miscible with water and soluble in most organic solvents. It is about twelve times as strong as acetic acid.

Many methods are available for making formic acid besides the general ones already listed. For example, a mixture of hydrogen and carbon dioxide can be transformed to it by means of the silent electric discharge, and sodium hydroxide and carbon dioxide will unite at 210° and 6 to 10 atmospheres pressure (Merz). By the general methods it can be made through hydration of hydrogen cyanide, by hydrolysis of chloral or chloroform, or by oxidation of methanol or formaldehyde. The usual laboratory procedure is the heating of oxalic acid with glycerin, an ester of these being a primary product.

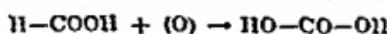


In its reactions formic acid differs markedly from other members of the series. These differences are attributable to the fact that it has only one atom of carbon but also mostly in that it is an aldehyde as well, as the

completely structural formula shows, H—O—C=O. From this point of view it can be named hydroxyformaldehyde. Dehydration by sulfuric acid and heat gives carbon monoxide instead of the usual anhydride.



Heating alone at 160° produces carbon dioxide and hydrogen; this may be carried out by catalytic agents like rhodium or palladium at room temperature. The most significant property, however, is its reducing character which is exhibited toward mild oxidizing agents such as silver or mercuric salts. The formic acid is thus converted to carbonic acid.



Formic acid finds employment in numerous industrial fields, notably the manufacture of dyes, dyeing operations, textile finishing, and tanning.

Acetic Acid U.S.P. is about a 36 per cent aqueous solution of CH_3-COOH , which obtains its name from the Latin, *acetum* or vinegar. Glacial

Acetic Acid U.S.P., the anhydrous form, is so named because it congeals at about 15° to an ice-like mass. **Diluted Acetic Acid N.F.** contains about 6 per cent. The anhydrous acid, which melts at 16.6° and boils at 118°, is miscible with water and organic solvents and is hygroscopic. The addition of water, probably to make the ortho acid, gives a rise in specific gravity from 1.0471 for the pure acid to 1.0681 for a 79 per cent mixture. With further addition of water, the specific gravity becomes lower, approaching 1.0000 for pure water.

Acetic acid, in the dilute solution (about 4 to 6 per cent) known as vinegar, is prepared by oxidation of ethyl alcohol with the aid of *Bacterium aceti* (mother of vinegar) at about 35°. The older methods, which required long periods for completion, have been shortened by modification but are essentially as originally devised. The dilute alcohol is allowed to trickle slowly over wood shavings which have previously been impregnated with mother of vinegar and dilute acetic acid. Under regulations of the Food and Drugs Act, "vinegar" must be made from apple juice, but vinegars are also made from wines, molasses, and other sugars and alcoholic solutions, and even by diluting acetic acid. Such products must be distinctly so labelled.

Concentrated acetic acid may be made by destructive distillation of wood. The products are charcoal, tar, gas, and an aqueous solution containing 6 to 8 per cent of acetic acid and about 1 per cent of methyl alcohol and 0.1 per cent of acetone. This brown "pyroligneous acid" is neutralized with lime and distilled to remove the water, alcohol, and acetone, leaving "gray acetate of lime." From the residue acetic acid can be liberated by mineral acids and distilled.

A method of obtaining the acid from acetaldehyde is fast superseding the older processes today. The catalytic hydration of acetylene to acetaldehyde produces the latter indirectly from calcium carbide. The oxidation is then carried out by air in the presence of metal oxides like that of manganese.

Acetic acid, directly or indirectly, is of immense value in industry. It is employed as solvent, in the manufacture of solvent esters, acetate rayon, dyes, white lead, and many other materials, as well as for vinegar, in medicine, and for the preparation of salts.

Propionic acid is a liquid with similar odor melting at -25° and boiling at 140°. It is miscible with water, but may be salted out as oil by saturating with salts like calcium chloride; hence, the name meaning "first fat."

Normal butyric acid, an official reagent, is found in rancid butter, where it gets its name, cheese, feces, and other decomposing materials. Butter contains a small quantity of its ester with glycerin and many plants contain esters with other alcohols. It is produced by fermentation of sugars or starch by *Bacillus butylicus* in the presence of calcium or zinc oxide.

Isobutyric acid occurs widely in the vegetable kingdom, as do also valeric and isovaleric acids and higher members of the series with an even number of carbon atoms.

Stearic and palmitic acids are common constituents of fats in the form of esters with glycerin. **Stearic Acid U.S.P.** is a mixture chiefly of these two, which are solids and almost insoluble in water. Cerotic and melissic acids are found as esters in waxes.

Caproic, diethylacetic, and n-butylethylacetic acids, as well as others, are now available in quantity. The first is advertised to sell (1938) at 35 cents per pound.

REVIEW QUESTIONS

1. By what other names is the acetic acid series known?
2. What is the characteristic group of acids? What is it called?
3. Write the formulas and specific names of acids in this series up to 5 carbon atoms and name each as a derivative of acetic acid and by the Geneva system.
4. How can acids be made from primary alcohols? from aldehydes? from trihalides? from esters? from cyanides? through the Grignard reagent? Write equations illustrating.
5. State two other common methods for synthesizing acids.
6. Write equations showing the formation of salts, of esters, of anhydrides, of acid chlorides, of amides, and for oxidation of acids.
7. How can an acid be reduced?
8. Why is halogenation of acids more useful than of the hydrocarbons? Write equation for chlorination of n-butyric acid.
9. What is an acyl radical? Write three specific formulas to illustrate and name each.
10. Name formic acid as an acyl derivative and as a derivative of formaldehyde.
11. What is the laboratory method of preparing it? State two other methods and write equations.
12. Wh
13. Wh
14. In
15. In what three ways is it manufactured commercially? Write equations.
16. Name the important acids of this series up to 30 carbon atoms and the source of each name. Which of them are official?
17. Why are those with an even number of carbon atoms more important than the others?
18. Starting with any compound of each class so far studied show how to convert it to a member of each of the other classes.

CHAPTER XII

ACID DERIVATIVES

SALTS

THE metallic salts are usually crystalline, soluble in water, and ionized as are the inorganic compounds. They are named as is usual by prefixing the metal name, changing the -ic to -ate, and dropping the term acid. Acetic acid gives sodium acetate and in general acetates, while propionic acid gives propionates. As has already been noted under acids, the salts are formed best by action of oxides or hydroxides but may also be made from the carbonates and other salts.

Reactions.—1. From the salts by action of mineral acids we may obtain the acids, which can then be filtered off if insoluble, extracted by organic solvents, or distilled if volatile.

2. Heated to a high temperature, the salts decompose to give ketones and a carbonate. For practical purposes the calcium or barium compounds are preferred.



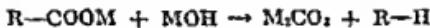
This reaction became of industrial importance when it was found possible to carry it out with acid vapors and with phosphorus pentoxide or oxides of metals as catalysts. Vapors of acetic acid passed over manganese oxide at 200° give acetone in high yield. The reaction can be used to produce mixed ketones, but naturally two simple ketones will be obtained simultaneously.

If the process is modified by making a mixture of salt with a formate, an aldehyde will be produced.



Again we will find our product mixed with the simple ketone from $R-COOM$ and carbon monoxide from the formate.

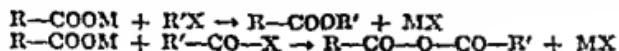
If the salt is heated with a base, a hydrocarbon may be the principal distillate.



Again a ketone may be formed simultaneously. The usual laboratory method for making methane is to heat sodium acetate with soda-lime or caustic soda.

Heating of the ammonium salt yields amide and cyanide. For this purpose dry distillation will suffice, but the yield is better if the heating is done in a sealed tube at higher temperature. It is also possible to perform the reaction by heating ammonium chloride with the sodium salt. (Chapters XVII and XVIII.)

3. With substances containing halogen heat gives metal halides and acyloxy compounds. With alkyl halides the product is an ester, with acyl halides an anhydride.



4. Electrolysis of soluble potassium salts gives a hydrocarbon in poor yield.



As secondary products are obtained alcohols and unsaturated hydrocarbons.

The formates are, like the parent acid, reducing agents. Heated alone they give an oxalate and hydrogen; with a base, a carbonate and hydrogen; with other salts, an aldehyde. Aluminum orthoformate is said to be an industrial product in Europe.

The acetates are of considerable importance because so many of them are widely used. The following are official:

Potassium Acetate U.S.P.

Sodium Acetate N.F.

Zinc Acetate U.S.P.

Lead Acetate U.S.P. (Sugar of Lead).

Solution of Ammonium Acetate N.F. (Spirit of Miadererus).

Solution of Lead Subacetate N.F. (Goulard's Extract).

Diluted Solution of Lead Subacetate N.F. (Lead Water).

Solution of Iron and Ammonium Acetate N.F. (Busham's Mixture).

Solution of Aluminum Acetate N.F. (Burrow's Solution).

Solution of Aluminum Subacetate N.F.

Those of copper, silver, cobalt, and uranium are used as reagents, while ferrous acetate and the chromium salt are employed as mordants. Basic copper acetate is referred to as verdigris and a mixture of it with copper arsenite is called Paris Green.

The acetates are identified by conversion to ethyl acetate or to cacodyl, or by means of ferric salts which give a red solution that precipitates a reddish basic salt on boiling.

Acid Ammonium Valerate N.F. occurs in crystalline plates with a strong odor of valeric acid which constitutes more than 60 per cent of the salt.

Zinc Stearate U.S.P. is a salt of the official acid and, therefore, contains some palmitate. It is a bulky, smooth powder used largely as a dusting medium for infants. Sodium stearate will be described under Soap (Chapter XIII).

Biliposol, a basic bismuth salt of what is claimed to be alphacarboxethyl-beta-methyl-nonoic acid, contains about 45 per cent of bismuth.

ESTERS

Esters may be defined as the compounds derived by condensation of acids and alcohols and have the formula $\text{R}-\text{COOR}'$. They are also referred to as ethereal or alkyl salts, but must be distinguished from inorganic esters and organic salts. They are widely distributed in nature, constituting a major share of fats and waxes and much of resins and volatile oils.

The simpler ones are named like inorganic esters and salts as alkyl formates, acetates, propionates, etc. Ethyl acetate, n-butyl butyrate, and isopropyl ethylmethylacetate are examples. The same procedure is followed for Geneva names; for example, methyl 2-chloropropanoate. In complicated compounds, acyloxy may be used as a prefix; thus methyl acetate would become acetoxymethane.

They are neutral liquids and solids, the lower ones being volatile and

pleasantly odorous, the higher less so. None of them is soluble in water or ionized, but the lower ones will dissolve to a limited extent. The most useful characteristics are the pleasant odor, neutrality, and ability to dissolve a variety of organic materials.

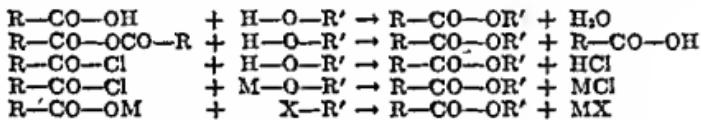
Preparation.—The process of manufacture is called esterification and usually involves some modification of the method indicated by the definition.

1. The direct action of alcohol and acid has already been discussed under reactions of the latter.

2. The anhydride or acyl chloride will give quicker and more certain results than the acid and is usually preferred. The operation is called acylation of the alcohol; most often it is performed by the acetyl derivatives and is then called acetylation.

3. Still more efficient but not often used is the reaction of acyl chloride on an alcoholate or the analogous metathesis of alkyl halide and organic salt.

The similarity of the several reactions in these three methods is apparent by comparing the equations.



Reactions.—1. The most useful chemical property of esters is their ability to hydrolyze, a reversal of the manufacture.

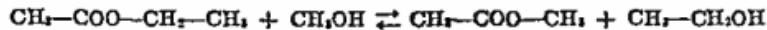


This may sometimes be accomplished by simple contact with water, more often with superheated steam, but unless one of the products is removed continuously it is never complete and always slow. Mineral acids or specific enzymes speed up the action by catalysis, although the end result is the same. Bases, however, carry the process slowly to completion, giving metal salts instead of the acids.

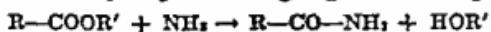


The velocity of reaction is proportional to the strength of the base. In the case of esters called fats the metal salt is known as a soap and the process saponification. There is by some a tendency today to entitle any hydrolysis of esters saponification and even to apply the term to hydrolytic decomposition of other kinds of compounds; in other words, hydrolysis and saponification are sometimes considered synonymous terms.

2. Alcoholysis, or a similar decomposition by alcohols, gives incomplete and reversible reaction, sometimes useful to make one ester from another.



3. Ammonolysis. Ammonia in concentrated solution acts on esters to produce amides. This may require a long digestion or higher temperatures.



4. Phosphorus pentachloride acts upon both parts of the ester to give an acyl chloride and an alkyl chloride.



5. The esters are reduced by sources of nascent hydrogen to the primary alcohol.



Since the acid itself cannot be converted in this way, this reaction provides a convenient method for reducing acids and gives fair yields. For two other important reactions of esters see Chapters XIV and XV.

In natural aromatic materials the esters are often the source of odor and flavor. Artificial materials to be used for perfumes and flavors can be concocted from blends of various esters, some of these mixtures being indistinguishable from natural substances. Ethyl n-butyrate, which is said to simulate the flavor of pineapple, is used in the largest quantity in these blends. Others employed in making artificial perfumes and extracts are: ethyl and isobutyl formates; ethyl, butyl, amyl, hexyl, and octyl acetates; amyl propionate; methyl, butyl, and amyl butyrates; ethyl and amyl isovalerates; ethyl nonoate; amyl undecanoate.

Many of these are also employed as solvents in the lacquer and other industries. More than a hundred solvent esters are now available and the list is being increased almost daily. Among these should be mentioned Glyceryl Triacetate U.S.P. (Triacetin), acetates of the glycols, cellosolves, and carbitols, and glyceryl monostearate.

Ethyl Acetate N.F. (Acetic Ether or Ester) is infrequently used in medicine and as a solvent in the industry and in the laboratory. It is a liquid with a pleasant, fruity odor and boils at 77°.

Vinyl acetate, $\text{CH}_2=\text{CH}-\text{O}-\text{CO}-\text{CH}_3$, is a raw material for manufacture of synthetic resins, while ethylidene diacetate, $\text{CH}_3-\text{CH}(\text{O}-\text{CO}-\text{CH}_3)_2$, is a solvent for nitrate and acetate rayon.

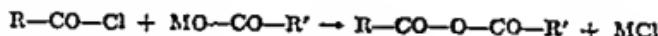
The waxes, obtained from plant and animal sources, are mixtures that contain chiefly esters together with some free alcohols. The esters are from higher acids of the acetic series and higher monatomic alcohols of the methanol series. They are solids more or less colored by impurities and melting below the boiling point of water, and they dissolve in ether, chloroform, or oils but are insoluble in water and sparingly so in cold alcohol. They are not readily hydrolyzed and, therefore, have no tendency to get rancid like the fats. Yellow Wax U.S.P. and its bleached form, White Wax U.S.P., contain chiefly the myristate of cetyl alcohol and some esters of cerotic acid. Spermaceti U.S.P. is largely cetyl palmitate, while carnauba wax contains myricyl cerotate with esters of carnaubyl alcohol, $\text{C}_{24}\text{H}_{48}\text{OH}$. Chinese wax is mostly cetyl cerotate.

ANHYDRIDES

Preparation.—1. The acyl oxides or acid anhydrides can be made by direct dehydration of the acid by means of powerful agents.

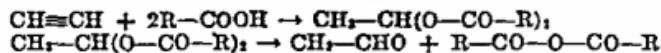


2. The more convenient laboratory method is by the action of acid chloride on metal salt.



As can thus be seen, this process may be used to yield mixed anhydrides.

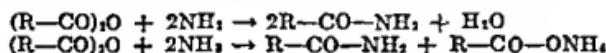
3. Ethylidene esters, which can be prepared by catalytic addition of acids to acetylene, decompose when heated to anhydride and acetaldehyde.



Reactions.—1. Addition of water converts the anhydrides to acids. This is a strongly exothermic reaction with acetic anhydride but becomes very slow with the higher compounds.

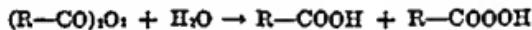
2. Alcohols are transformed into esters (acylation or esterification) by these anhydrides more easily than by the corresponding acids. This was fully discussed under preparation of the esters.

3. Ammonia, as well as primary and secondary amines (q. v.), condense with the anhydrides to form amides, or amides and ammonium salts, depending on conditions.

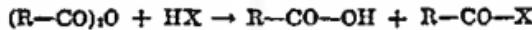


4. Reduction of the anhydrides with nascent hydrogen proceeds as with esters to give primary alcohols.

5. Hydrogen peroxide or metallic peroxides convert them to acyl peroxides which with water yield acids and their peroxides, but the latter are too unstable to be isolated.



6. Heated with the strong hydrohalogen acids, they are decomposed into acids and acyl halides.



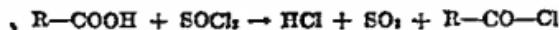
The halogens, on the other hand, bring about substitution in alpha position as with acids.

Acetic anhydride is described as an official reagent because it is very useful in the laboratory for acetylations. It is today an important article of commerce, since it is necessary in the manufacture of acetate rayon and in the preparation of many solvent esters.

The acyl peroxides were introduced into medicine years ago with the idea that they would be good oxidizing agents and, therefore, bactericides. All of them are unstable and very liable to explode in handling, so the idea was later abandoned. Acetylbenzoyl peroxide was known as Acetozone and succinyl peroxide as Alphozone. Benzoyl peroxide, which will be mentioned later, is occasionally used today.

ACID CHLORIDES

The acyl chlorides are fuming liquids with boiling points lower than those of the related acids. Corresponding bromides and iodides are known but unimportant. The chlorides may be prepared by action on the acid of phosphorus pentachloride or trichloride, or of thionyl chloride which has the advantage of furnishing only sulfur dioxide and hydrogen chloride as other products.



They also may be made by the reaction of dry chlorine on aldehydes, or of hydrohalogen acids on anhydrides.

Reactions.—1. With water they are violently converted to acid and hydrogen chloride; the fuming in air is caused by the last named.

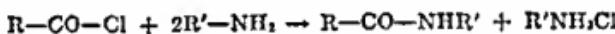


2. Alcohols are converted very easily to esters in a similar way (alcoholysis).



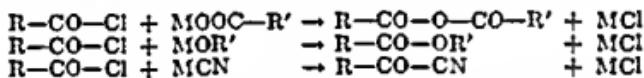
In esterifying alcohols acetyl chlorides are much the most efficient agents. The process of acetylation by means of acetic acid or its anhydride, or best by acetyl chloride, is utilized to identify compounds containing hydroxyl groups and determine their amounts. In this reaction primary alcohols are the most easily esterified, tertiary least.

3. Ammonia or ammonium carbonate reacts to form amides more readily than these are formed from acid or anhydride. The acetyl group can also be introduced into ammonia derivatives in the same way.



4. Reduction to primary alcohol by nascent hydrogen proceeds as with esters or anhydrides.

5. As with the alkyl halides, metathetical reactions with metallic compounds are often useful in synthesis. As examples might be mentioned heating with metal salts to produce anhydrides, with alcoholates to yield esters, and with cyanides to give ketonic nitriles.



For reaction with metals like magnesium see Chapter XX.

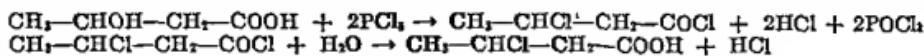
Acetyl chloride is the only substance of this class that is commonly used in the laboratory. It is a fuming, colorless liquid boiling at 52°. Formyl chloride is unknown, but chlorides of many of the other acids have been prepared.

HALOGEN ACIDS

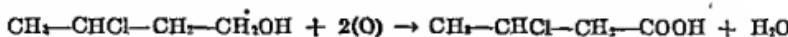
Preparation.—As was noted in reactions of the acids, chlorination of these proceeds smoothly to substitute for hydrogen in alpha position. A second atom of halogen can be introduced with greater difficulty. The trichlor compound from acetic acid may be made by oxidizing chloral, but no more chlorination can take place in the other acids because there is no further alpha hydrogen. The replacement by bromine can also be accomplished by carriers or a high temperature, while iodine will substitute if iodine acid or other agent is added to react with the hydrogen iodide that is produced. In all cases the simultaneous treatment with phosphorus or sulfur assists the halogenation by previous formation of the acyl halide, since the latter is more easily affected by halogen.

The beta and gamma compounds can be prepared in other ways. Addition of hydrohalogens to unsaturated acids takes place in such a way that hydrogen goes nearest to the carboxyl group. With hydrogen chloride $\text{CH}_2=\text{CH}-\text{COOII}$ yields $\text{CH}_2-\text{CHCl}-\text{CH}_2-\text{COOII}$ and not $\text{CH}_2-\text{CH}_2-\text{CHCl}-\text{COOII}$. Another means for preparing them is by

action of phosphorus halides or of hydrohalogens on lactones, hydroxyacids, or their nitriles.



Oxidation of halogen alcohols or aldehydes can also be used.



Reactions.—The halogen acids will naturally possess the properties of halides and of acids, but with some modifications. The halogen atom is even more reactive than in the alkyl halides and confers upon the carboxyl group more acid properties, so that the compounds are much stronger than acids of the acetic series.

Moist silver oxide produces hydroxyacids, as do also aqueous solutions of strong bases, although subsequent alteration of these hydroxyacids is common.

Chloroacetic acid, a crystalline solid melting at 62° , is roughly 1000 times as strong as the parent acetic acid. It is made by direct chlorination of the latter. Large quantities are used in synthetic processes, both industrially and on a laboratory scale.

Dichloroacetic acid melts at 11° and boils at 194° . It is much stronger (thirty times) than the mono compound.

Trichloroacetic Acid U.S.P., melting at 57° and boiling at about 200° , is manufactured by oxidizing chloral. It is nearly if not entirely as dissociated as the strong mineral acids.

Calcium Iodobehenate U.S.P. (Sajodin, Calioben), the calcium salt of an iodohehenic acid, is used for its iodine content.

Stearodine N.N.R., a calcium iodostearate, is used similarly.

Sahromin (Calbroben), the calcium salt of a dibromobehenic acid, is employed in medicine like the other bromides.

Lipoiodine N.N.R. is described as the ethyl ester of diiodobrassidic acid. It is made by adding iodine to ethyl brassidate, an unsaturated ester, but the product is a diiodo substitution product of ethyl behenate, $\text{CH}_3\text{—}(\text{CH}_2)_n\text{—CHI—CHI—}(\text{CH}_2)_n\text{—COO—CH}_2\text{—CH}_3$.

UNSATURATED ACIDS

Compounds with a double bond in addition to the carboxyl group might be expected to have the properties of both. This is indeed the case, although the presence of one somewhat modifies the properties of the other. The most important member of the series is oleic acid, which gives its name to the group as a whole.

In general the members have a much lower melting point than the corresponding saturated acids. Indeed, the common ones in fats, including oleic, are liquid, while stearic and other fatty acids of the acetic series are solids.

Preparation.—The methods to be used are those that could be predicted in view of the ones given for unsaturated hydrocarbons and for the acids. In general, these require no special discussion at present.

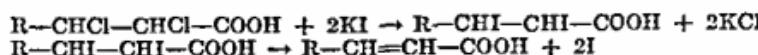
1. Oxidation of unsaturated, primary alcohols and aldehydes.

2. Hydrolysis of unsaturated esters, cyanides, and Grignard compounds.

3. Through the acetoacetic or malonic ester syntheses, using unsaturated halides.

4. Withdrawal of hydrogen halide from halogen acids by means of alcoholic alkali. This proceeds fairly well with alpha derivatives and more readily with beta; in both cases the double bond takes the alpha-beta position. Hydroxyacids or their lactones are given with gamma and delta compounds.

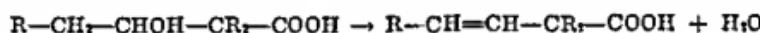
5. A similar process removes halogen from alpha-beta dihalides by means of metals, nascent hydrogen, or even more readily by heating with potassium iodide which first forms the diiodide and then loses the halogen.



6. Withdrawal of water from beta-hydroxyacids gives unsaturated acids with the double bond in alpha-beta position.



If both alpha hydrogens have previously been substituted the withdrawal is from gamma position.



Reactions.—As has been observed, we can expect little new in properties, having now those of the double bond and also those of the carboxyl group. Two important modifications might be noted. Additions to the double bond take place in such a way that the negative group goes further from the carboxyl. With hydrogen chloride, for example, $R-\text{CH}=\text{C}(\text{CH}_3)-\text{COOH}$ gives $R-\text{CHCl}-\text{CH}(\text{CH}_3)-\text{COOH}$ and not $R-\text{CH}_2-\text{CCl}(\text{CH}_3)-\text{COOH}$ as was the rule with unsaturated hydrocarbons. Again, the presence of an alpha double bond retards or prevents esterification of the carboxyl group.

Acrylic or propenoic acid, $\text{CH}_2=\text{CH}-\text{COOH}$, is a liquid boiling at 142° and miscible with water. It may be made by oxidation of allyl alcohol or acrolein by silver oxide; by adding bromine to allyl alcohol, oxidizing to the dibromopropionic acid, and removing bromine by zinc; by distilling beta-iodopropionic acid with lead oxide.

Crotonic acid, $\text{CH}_3-\text{CH}=\text{CH}-\text{COOH}$, which receives its name from croton oil, occurs in pyroligneous acid. Its geometric isomer is called isocrotonic acid. Methylacrylic acid, $\text{CH}_2=\text{C}(\text{CH}_3)-\text{COOH}$, and vinyl-acetic acid, $\text{CH}_2=\text{CH}-\text{CH}_2-\text{COOH}$, are isomeric. The latter, when boiled with potassium hydroxide or acids, tautomerizes to crotonic acid.



Angelic (angelica) and tiglic (croton oil) acids are geometric isomers with the formula $\text{CH}_2-\text{CH}=\text{C}(\text{CH}_3)-\text{COOH}$. They are found in a number of volatile oils.

Hypogaeic acid, $\text{CH}_3-(\text{CH}_2)_r-\text{CH}=\text{CH}-(\text{CH}_2)_s-\text{COOH}$, is contained as ester in peanut oil.

Oleic Acid U.S.P. is chiefly $\text{CH}_3-(\text{CH}_2)_r-\text{CH}=\text{CH}-(\text{CH}_2)_s-\text{COOH}$. It occurs as glyceryl ester in nearly all fats and is the most common of all fatty acids, although it is not of the acetic or fatty acid series. Its name is derived from olive oil. Nitrous acid converts it to claidic acid, a

stereo-isomer. Iso-oleic acid is presumed to have the double bond in a different position.

Lead oleate is the chief component of the plaster and ointment described in the formulary. Oleate of Mercury U.S.P. is made from mercuric oxide and oleic acid. Oleo-Bi is presumed to be a suspension of bismuth oleate in olive oil.

Erucic acid, $\text{CH}_3-(\text{CH}_2)_7-\text{CH}=\text{CH}-(\text{CH}_2)_n-\text{COOH}$, is found in the oils of rape and mustard. Nitrous acid converts it to the geometric isomer, brassidic acid.

The chief acid constituent of castor oil is ricinoleic acid or hydroxyoleic acid, $\text{CH}_3-(\text{CH}_2)_5-\text{CHOH}-\text{CH}_2-\text{CH}=\text{CH}-(\text{CH}_2)_7-\text{COOH}$.

Members of the linoleic series of acids contain two double bonds. The most important one is linoleic or linolic acid, $\text{C}_{18}\text{H}_{32}\text{O}_2$, which is very common in vegetable oils: Sorbic acid, $\text{CH}_3-\text{CH}=\text{CH}-\text{CH}=\text{CH}-\text{COOH}$, is present in the unripe sorb apple.

Linolenic acids, $\text{C}_{18}\text{H}_{30}\text{O}_2$, which contain three double bonds, are characteristic of linseed oil.

Propiolic, $\text{CH}=\text{C}-\text{COOH}$, and tetrolic, $\text{CH}_3-\text{C}=\text{C}-\text{COOH}$, acids are members of another series containing the triple bond.

Iodostarine N.N.R. (Diiodotaric Acid), $\text{C}_{12}\text{H}_{21}\text{I}_2\text{COOH}$, is used like the other organic compounds of iodine.

REVIEW QUESTIONS

1. Write equations for heating salts alone; with formates; with bases; ammonium salts alone; formates alone; formates with bases.
2. What substance is produced by oxidation of a formate?
3. Which of the acetates are official and in what forms?
4. What are sugar of lead, Goulard's extract, lead water, spirit of Mindererus, Basham's mixture, verdigris, Burow's solution and Paris green?
5. What valerate and what stearates are official?
6. Write the general formula of an ester. State three ways of preparing an ester (esterification) from the alcohol and write equations.
7. What are the processes of acylation and acetylation? How are they performed? For what purposes? Write equations.
8. Write equations for saponification of an ester by acids and by bases.
9. How do the esters behave when reduced? with phosphorus pentachloride? with ammonia? Write equations.
10. Name an official ester of the acetic series.
11. Illustrate two methods for making acetic anhydride.
12. How are acyl chlorides made? Write an equation.
13. How do they behave in acylation? upon reduction? Write equations to illustrate.
14. Write formulas of butyryl chloride, valeryl bromide, trichloroacetic acid, alpha-bromopropionic acid, and alpha-beta-dibromobutyric acid.
15. What is produced in halogenation of an acid?
16. What are Calioben, Sabromin, Stearodine, Lipoiodine, Iodostarine?
17. Enumerate four ways to prepare an unsaturated acid and write equations to illustrate each.
18. What compound is formed by adding hydrogen chloride to 2-methyl-3-hexenoic acid?
19. Write formulas of acrylic, crotonic, and oleic acids.
20. What are propiolic, ricinolic, linoleic, and linolenic acids?

CHAPTER XIII

FATS AND SOAPS

The fats are natural animal or vegetable substances that are chiefly triglycerides (glycerides) of so-called fatty acids, $\text{CH}_2(\text{OOCR})-\text{CH}(\text{OOCR}')-\text{CH}_2-\text{OOCR}''$. While these acids frequently belong to the acetic series, which is also called the fatty acid series, yet the term as used here covers several others. Those which occur most commonly as glycerides in natural fats are oleic, linoleic, stearic, palmitic, and linolenic; less often are encountered myristic, lauric, caproic, caprylic, capric, butyric, arachidic, behenic, and some others. Some acids are found characteristic of special fats and will be mentioned later.

Seldom do we have means of ascertaining the exact composition of fats, even if we ignore all extraneous matter and examine only the glyceryl esters. While a given fat upon hydrolysis may produce certain acids and glycerin, yet there is no way to determine whether the material contained a mixture of simple esters with 3 molecules of an individual acid to 1 molecule of glycerin, or whether it contained mixed esters with more than one acid combined with a single molecule of glycerin. Nevertheless, we often refer to theoretical combinations by names, such as triolein or olein which refers to an ester with 3 molecules of oleic acid, and alpha-palmito-distearin which should be self-explanatory.

The vegetable fats are usually liquid and for this reason are called fixed oils, but the official theohroma oil is a notable exception. On the other hand, animal fats are all solids with the exception of a few like the marine liver oils. The melting point is proportional to those of the constituent acids and these in turn vary with the amount of unsaturation. Those fats that contain a high percentage of unsaturated acids like oleic, linoleic, and linolenic have the lowest melting points, while those that are composed chiefly of saturated acids like stearic or palmitic are solid.

Other physical properties vary with source and purity. The color may
be yellow, orange, or brown.
The index of refraction varies with the organic
solvents, notably ether and benzene, but are insoluble in water and only
partially in alcohol.

Reactions.—1. Heat decomposes the fats before the boiling point is reached, giving as primary products fatty acids and acrolein. The latter accounts for the acrid odor that is noted in cooking when these substances are subjected to fairly high temperature.

2. Rancidity, accompanied by disagreeable odor and taste, results from the combined action of moisture, air, light, and warmth. While this change is often said to be plain hydrolysis to form fatty acids, yet true rancidity comes only by the combined action of all four factors, especially from oxidation of double bonds in the unsaturated acids by atmospheric oxygen.

3. As is the case with other esters, the fatty acids are easily hydrolyzed to glycerin and the ac-

water for many hours or by treatment with superheated steam, but it is more usual to use an assisting agent. Nature often provides an enzyme (lipase) for this purpose, as in the digestive processes of animals or in the metabolism of plants. In industry or in the laboratory we could use such enzymes, but it is customary to employ the catalytic mineral acids, or better alkalies which remove the acid product by forming soaps (saponification) and thus perform the hydrolysis rapidly and completely.

4. Hydrogenation of fats results in increased saturation with the resultant higher melting point. The vegetable oils can thus be made more or less solid to produce satisfactory substitutes for lard or butter, at least in some respects. The process is carried out with ordinary hydrogen in the presence of catalysts like palladium, platinum, or especially nickel.

Analytical.—The laboratory examination of fats for purity and identity necessitates numerous tests because the various commercial articles are so alike in composition and because there are so many that may be encountered. Although it is usual to determine physical constants, such as melting point, specific gravity, and index of refraction, these throw very little light on the problem, because there is so little variation; for example, the specific gravity is lowest in colza oil (0.913) and highest in linseed oil (0.941). No attempt can be made here to describe all of the numerous tests to which a fat may be subjected, but those few that are described in the Pharmacopoeia will be mentioned.

The acid and ester numbers are expressed in milligrams of potassium hydroxide required respectively to neutralize any free acid and hydrolyze the esters in 1 gram of fat. The acids are first neutralized directly by standard alkali in alcoholic solution, and the requisite calculation is made. A sufficient excess of the base is then added, and the whole is heated on a steam bath until the reaction is complete, when the excess is determined by titration, and the ester number is calculated. The saponification number represents the sum of the acid and ester numbers, or the milligrams of potassium hydroxide necessary to neutralize acids and saponify esters.

The iodine value represents proportionate unsaturation and is expressed as the percentage of iodine that can be absorbed. Its determination is carried out by adding an excess of the halogen, allowing to stand for thirty minutes, and titrating the amount unconsumed by means of standard thiosulfate. The Pharmacopoeia directs for use (Hanus method) a solution of iodine and bromine in glacial acetic acid.

The unsaponifiable residue is found by extracting it with ether from the solution after saponification and weighing directly. In natural fats the amount is seldom over 1 per cent, chiefly sterols, and any higher figure is just cause for suspicion that adulteration has been made. The usual unsaponifiable adulterant is petroleum or its fractions.

Drying Oils.—These are useful for the manufacture of paints, since they become oxidized when exposed to air to give resin-like substances. Their iodine value is proportionally high because the drying power depends upon unsaturation, mainly attributable to isomeric linolenic acids. Linseed Oil U.S.P. is most in demand, not because it is most unsaturated, but because it dries fairly quickly to produce a hard, tough, uniform, and durable residue. Commercially the speed of drying is increased by previous treatment with a drier (oxide or salt of metals) at elevated temperature (boiled linseed oil); by partially oxidizing by air at about 70° (blown oil); or by

adding the drier at ordinary temperature (tung oil). The official (raw) oil must not be so treated.

Tung oil (Chinese or Japanese wood oil), obtained from the seeds of *Aleurites cordata*, is the most rapidly drying oil known, but it is inferior because the residue has undesirable qualities. The amount of industrial use seems to vary directly with the market price of linseed oil.

Walnut oil, from the kernels of *Juglans regia*, gives a very fine and durable residue and is employed in artists' paints. Other commercial drying oils are hempseed from *Cannabis sativa*, sunflower seed, and poppy seed.

Semidrying Oils.—These have a fairly high iodine value but do not give satisfactory drying for use in paint. Cottonseed Oil U.S.P. is much used because of its cheapness in the hydrogenation process to produce substitutes for lard and butter. Oridine N.N.R. is an iodized product of the oil, as is usually Iodized Oil U.S.P. Corn oil is also cheap and much used for hydrogenation. Others in this class are Sesame Oil N.F., that from kapok, and that from the soy bean. The last is being grown in increasing quantities in the United States because of the numerous products that can be made from it.

Non-drying Oils.—The articles in this class have an iodine value below 100 and, although the chief constituent is usually olein, they are fairly stable upon exposure. Olive Oil U.S.P. is pressed from the cold fruit (virgin), but poorer grades may be made by pressing hot or even by extraction. Expressed Almond Oil U.S.P. and Persic Oil U.S.P. are similar in composition and properties, as are also products from the peanut and others.

Theobroma Oil U.S.P. (Cocoa Butter) has a very low iodine value, as one might expect considering its high melting point of 30° to 35°. Other commercial fats like it are cocoanut oil, palm oil, and palm nut oil. The first of these contains notable amounts of insoluble, volatile acids like caprylic and capric and is often used to make vegetable margarines.

Castor Oil U.S.P. contains chiefly a glyceryl ester of ricinoleic acid having an hydroxyl group. The relative amount of such a compound is determined by finding an acetyl value, ascertained from the amount of acetic anhydride or acetyl chloride necessary for esterification. Dehydrated castor oil, sold under the title of Dehydrol, has a fairly high degree of unsaturation and can be used as a drying oil. Riodine N.N.R. is an iodized castor oil.

Croton Oil N.F. contains the usual esters of glycerin but its unique purgative action is apparently due to a small quantity of a resin. Chaulmoogra Oil U.S.P. is composed largely of glyceryl esters of chaulmoogric and hydnocarpic acids, which are cyclic in character, and will be discussed later. Rapeseed or colza oil is much employed in industry and fats from mustard are like it in composition.

Animal Fats.—These are almost all solids or semisolids, contain little unsaturation, and show no tendency to dry. Important are Lard U.S.P. and Prepared Suet U.S.P. Butter, which has an especially heterogeneous composition, contains up to 6 per cent of butyric ester, although the chief acid is palmitic. Among other oils in this group that are sold in commerce are those from neatsfoot, whale, sperm, and bone.

The marine liver oils, such as those from the cod, burbot, halibut, percomorph, or shark, are notable in containing much of vitamins A and D.

Cod liver oil has some glycerides of the usual acids, but also some peculiar ones, one at least containing nitrogen. The other marine liver oils are probably similar.

There should also be mentioned here certain other lipids (fatty substances) that are found in animal and vegetable bodies. Especially important are lecithins and cephalin which make up a portion of cerebral and nervous tissue. They hydrolyze to glycerin and the usual fatty acids, but give in addition phosphoric acid and certain nitrogenous compounds. These will be discussed in greater detail in Chapter XVII.

Soaps.—These may be defined as metallic salts of the acids from fats. Except for those of the alkalies, however, they are insoluble in water, and the commercial varieties are all salts of sodium or potassium. The unsaturated fats and potash tend to give soft products, while the harder fats and soda yield much more solid ones. By varying the amounts, one can obtain a liquid material such as Soft Soap U.S.P., which is made from potassium hydroxide and linseed oil, or more solid substances up to Hard Soap U.S.P. (Castile) from olive oil and sodium hydroxide. Sodium Stearate U.S.P. is a hard variety made from a mixture of saturated acids.

Salts of fatty acids with metals other than the alkalies are insoluble in water, so that hard waters that contain compounds of calcium and magnesium use up soap by precipitation. In order to obviate this difficulty there have been devised various soaps, emulsions, and wetting agents. RO-SO₂-ONa, or "..." for making stable emulsions of oils with aqueous solutions and for other purposes.

Plaster of Lead Oleate N.F., Ointment of Lead Oleate N.F., and Oleate of Mercury U.S.P. are official preparations of insoluble soaps.

While the manufacture of soap is theoretically very simple, it is technically more complicated than would seem. The saponification is carried out by emulsifying with a portion of the necessary alkali and later boiling with the full amount. The product is later salted out from the aqueous solution, mixed with the desired additions, and pressed into cakes or dried to a powder or flakes. Transparency is attained by incorporating alcohol or glycerin and there may also be added perfumes, colors, medicaments like sulfur or phenols, fillers like clay, abrasives such as sawdust or pumice, rosin salts, alkalies or wetting agents, solvents like naphtha, etc.

On account of the conglomerate and variable composition of soap, laboratory examination for purity may be a long process. Although the value in cleaning and emulsifying is due to gradual liberation of alkali by hydrolysis, yet added or excessive alkali is objectionable. Unsaponified fat, free acids, water, adulterants added to make weight are examples of the substances for which tests must be made.

REVIEW QUESTIONS

1. What is a fat? triolein? stearin? fixed oil?
2. "
3. "
4. "
5. What happens when an oil becomes rancid?
6. Define acid, ester, and saponification numbers and iodine value.

7. Name two good drying oils, two official semidrying oils, five official non-drying oils, and two official animal fats.
8. What is peculiar about the composition of castor, croton, cocoanut, and cod liver oils and butter?
9. Of what is the acetyl value a criterion?
10. What is a soap? How is it manufactured?
11. Why does hard water use up soap? What substances are contained in hard water soaps?
12. Name four other kinds of substances commonly added to commercial soaps.
13. If a solution of soap is acidified what is the precipitate that is formed?
14. What is the difference between boiled and official raw linseed oils?



CHAPTER XIV

HYDROXY-ACIDS AND RELATED COMPOUNDS

BEFORE taking up the subject indicated in the heading above, it will be well to summarize the oxygenated compounds we have already discussed and make a survey of other possibilities. With increasing amount of hydroxyl substitution, there is a great variety of possible compounds. For a single hydroxyl group to a carbon atom we find modified properties of alcohols; for each two such groups to a carbon atom, we obtain the carbonyl group typical of aldehyde or ketone; and for three we have the carboxyl radical of acids. Combinations of these three structures give rise to numerous classes, increasing in variety and complexity as the amount of substitution rises. The following table presents all examples through those having five hydroxyl groups, and the student can easily continue the list for further compounds. For convenience chapter numbers and examples are given for some of the classes.

	CHAPTER	EXAMPLE
One Hydroxyl		
1. Alcohols	VI	Ethanol
Two Hydroxyls		
1. Glycols	VIII	Ethylene Glycol
2. Aldehydes	IX	Acetaldehyde
3. Ketones	X	Acetone
Three Hydroxyls		
1. Glycerols	VIII	Glycerin
2. Hydroxy-aldehydes	IX	Glycolic Aldehyde
3. Hydroxy-ketones	X	Acetol
4. Acids	XI	Acetic Acid
Four Hydroxyls		
1. Erythrins	VIII	Erythritol
2. Dihydroxy-aldehydes	IX	Glyceric Aldehyde
3. Dihydroxy-ketones		
4. Dialdehydes	IX	Glyoxal
5. Diketones	X	Diacetyl
6. Keto-aldehydes		
7. Hydroxy-acids	XIV	Lactic Acid
Five Hydroxyls		
1. Pentatomic Alcohols	VIII	Arabitol
2. Trihydroxy-aldehydes	XXII	Erythritose
3. Trihydroxy-ketones	XXII	
4. Dihydroxy-acids	XIV	Glyceric Acid
5. Hydroxy-dialdehydes		
6. Hydroxy-diketones		
7. Hydroxy-keto-aldehydes		
8. Aldehydo-acids	XIV	Glyoxylic Acid
9. Keto-acids	XIV	Acetoacetic Acid

It is not necessary to discuss each of the possible classes, because practically no important new principles or properties would be disclosed and because in many of them none of the known compounds is of interest to us. After a description of the monohydroxy-acids, a few representatives of other classes will be noted, including some which are not in the table. Later chapters will describe some of those that have a greater amount of hydroxyl substitution.

Those compounds that contain a single hydroxyl group and a carboxyl radical might reasonably be expected to have properties of alcohols and

of acids, and this is indeed the case. Nevertheless, one of these groups influences somewhat the usual properties of the other, although such modifications tend to disappear as the distance between them is increased. Therefore, it is important to note the position of the hydroxyl in relation to the carboxyl, and this is expressed in naming the compounds by letters of the Greek alphabet, such as alpha-hydroxypropionic acid. The Geneva system directs use of the prefix hydroxy- and assumes that the carboxyl group is number 1.

The acids belonging to this series are liquids and solids that usually cannot be distilled without decomposition, except under reduced pressure. They are more readily soluble in water than the corresponding fatty acids and less soluble in ether.

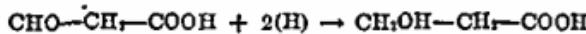
Preparation.—Methods for making these compounds are but the several ones for alcohols on the one hand and acids on the other. A complete list of them, such as is given in large reference books, is here unnecessary because nothing new is involved. A few of them are stated, each with an illustrative equation.

1. Oxidation of glycols one of whose hydroxyls is primary; a hydroxy-aldehyde is intermediate.

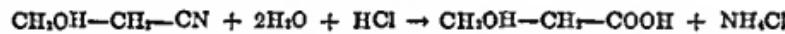


The other hydroxyl may also oxidize but one can keep this at a minimum by controlling conditions.

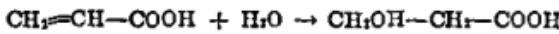
2. Reduction of aldehydo-acids, keto-acids, or derivatives of dibasic acids.



3. Hydrolysis of esters, nitriles, or amides.



4. Hydration of unsaturated acids by mineral acids or aqueous alkali.



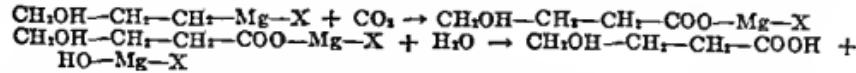
5. Reaction of monobalogen acids with moist silver oxide, dilute alkalies, or even water.



6. Reaction of nitrous acid on amino acids.



7. Using the Grignard reagent, from hydroxyalkyl halides, with carbon dioxide.



The synthesis of hydroxy-acids by means of acetoacetic or malonic esters is also useful.

Reactions.—1. As has been mentioned, we find properties of acids and of alcohols. For example, phosphorus pentachloride will convert them by action on both groups to monochloro acid chlorides.

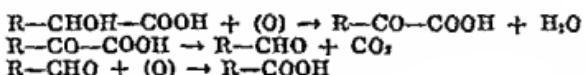


2. Hydrogen iodide reduces the hydroxyl to produce an acid of the acetic series.

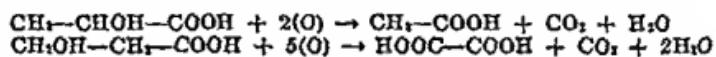


3. Either group can form metal salts, and either can be converted into esters, one by acylating agents, the other by alcohols.

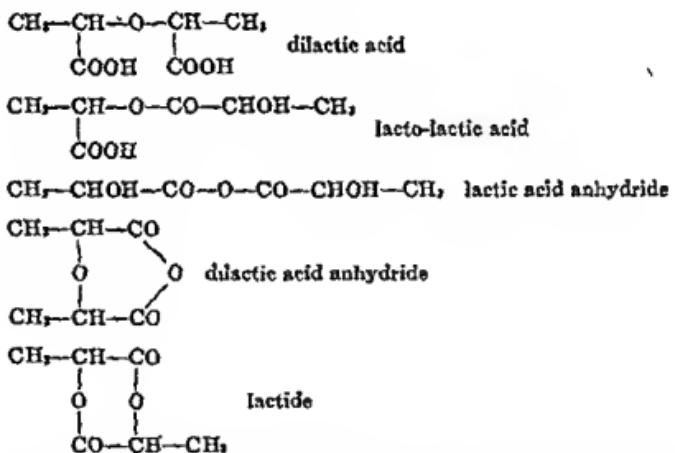
4. In other directions we find modifications of the type reactions. The alcohol carbon can be oxidized if primary or secondary as usual, but this takes place more readily because the carboxyl group is present. Furthermore, the carboxyl group shows considerable tendency to lose carbon dioxide, a trait almost entirely lacking in the fatty acids.



Thus, alpha-hydroxypropionic acid oxidizes to acetic and carbonic acids, while the beta compound gives oxalic and carbonic acids.

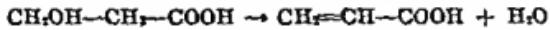


5. The products of dehydration depend on position of the hydroxyl group. The alpha compounds form five different types of anhydrides, and these together with names are illustrated by lactic (alpha-hydroxypropionic) acid, $\text{CH}_3-\text{CHOH}-\text{COOH}$.



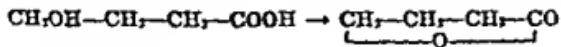
It will be noted that the processes of dehydration here are partly esterification, partly acid anhydride formation, and partly the making of ethers.

Beta-hydroxy-acids often lose water to give an unsaturated acid, entirely analogous to the dehydration of alcohols to olefines.



The double bond may assume alpha-beta position as given or sometimes beta-gamma.

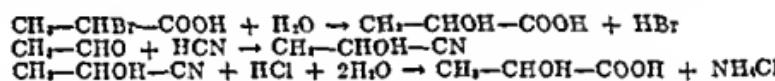
Gamma-hydroxy-acids and delta-hydroxy-acids easily lose water, often spontaneously, to produce lactones.



These lactones or inner anhydrides are often found in vegetable and animal materials and in the products of oxidizing them. They are converted to salts of the acid by strong alkali, but not by the carbonates, and are but incompletely hydrated by boiling with water, especially those from the gamma-acids. The alpha and beta compounds will also sometimes furnish unstable lactones.

Glycollic acid, $\text{CH}_2\text{OH}-\text{COOH}$, the simplest of these hydroxyl compounds, is found quite widely in nature, especially in unripe fruits, sugar cane, beet juice, and many green leaves. It is a crystalline solid melting at 80° , is very soluble in alcohol or water, and is nearly as strong as formic

($\text{CH}_2-\text{CHOH}-\text{COOH}$), $\text{CH}_2-\text{CHOH}-\text{COOH}$, is described as a hygroscopic, syrupy liquid that is miscible with water and contains anhydrides. It occurs in opium, sauerkraut, pickles, gastric juice, sour milk, and other partly fermented material, and can be prepared by fermentation of sugars and starch through agency of the lactic bacillus. Synthetically it may be made by any of the general methods, probably most readily from alpha-bromopropionic acid or from acetaldehyde by addition of hydrogen cyanide.



Lactic acid decomposes readily when heated or treated with various reagents, giving anhydrides, carbon monoxide, formic acid, or other products. Oxidation converts it to pyruvic acid, acetaldehyde, and acetic acid; $\text{C}_2\text{H}_5-\text{CO}-\text{COOH}$, CH_3-CHO , and CH_3-COOH respectively.

In commerce 80 to 90 per cent of the marketed lactic acid finds employment in the leather industry, but it is also used in dyeing, in calico printing, as a flavor and preservative, in baking powders, as milk modifier for infants, and in many other ways. Several of the salts are used in medicine: Calcium Lactate U.S.P., $\text{Ca}(\text{C}_3\text{H}_5\text{O}_2)_2 \cdot 5\text{H}_2\text{O}$, Ferrous Lactate N.N.R., and Silver Lactate N.N.R. Sodium *D*-lactate N.N.R. is used to make media for blood replacements, a sixth-molar solution being about isotonic with the blood. The ethyl ester is considered a good solvent for nitrocellulose lacquers.

Although the formula of lactic acid contains an asymmetric carbon atom, the product of fermentation or of synthetic processes is optically inactive. However, it can be resolved into its active components by crystallization of morphine or strychnine salts and by other methods.

Sarcolactic acid (paralactic acid), the dextro form, is a product of muscular exertion in animals and, hence, is found in muscle, blood, urine, and other animal secretions and organs. It can be prepared as a by-product in butyric fermentation. The corresponding levo compound can be made by resolution of the racemic or as a product of fermentation by the *L*-lactic bacillus. The zinc salt rotates the plane of polarization to the right, while zinc sarcolactate rotates it to the left. This is but one instance of the Walden inversion of optical rotation after simple chemical changes.

Beta-lactic acid (ethylene-lactic or hydracrylic acid), $\text{C}_2\text{H}_5\text{OH}-\text{CH}_2-$

COOH, is isomeric with the alpha compound. It oxidizes to oxalic acid, HOOC—COOH, and easily loses water to form acrylic acid. Beta-hydroxybutyric acid, CH₃—CHOH—CH₂—COOH, often called beta-oxybutyric acid, is a product of abnormal metabolism of carbohydrates in the body and is found in the urine of diabetics.

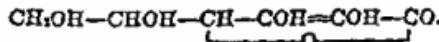
Ricinoleic acid, CH₃—(CH₂)₅—CHOH—CH₂—CH=CH—(CH₂)₇—COOH, as an ester with glycerin, constitutes a large portion of castor oil.

POLYHYDROXY ACIDS

Glyceric acid, CH₂OH—CHOH—COOH, is a syrupy liquid formed during the decomposition of nitroglycerin and can be prepared by controlled oxidation of glycerin. From such a source it is racemic but may be resolved into its optically active forms. Erythritic acid, CH₂OH—CHOH—CHOH—COOH, is the corresponding oxidation product of erythritol, while arabonic acid, CH₂OH—(CHOH)₂—COOH, is obtained from arabitol. They contain two and three asymmetric atoms of carbon respectively.

Gluconic acid, CH₂OH—(CHOH)₄—COOH, is now prepared by the catalytic oxidation of dextrose (d-glucose), from which is derived its name. It is but 1 of the 16 isomers that have this formula, possible because there are 4 asymmetric carbon atoms; a discussion of the reasons for this many isomers will be made in the chapter on carbohydrates. Mannonic, gulonic, galactonic, talonic, and idonic acids are isomers that have been prepared. Calcium Gluconate U.S.P., Ca(C₆H₁₁O₆)₂·H₂O, is a convenient salt for administering calcium and has practically supplanted the lactate or chloride. Ferrous gluconate may be used similarly for iron.

Ascorbic Acid U.S.P. (Cevitamic Acid N.N.R., Vitamin-C) is an unsaturated gamma-lactone with the formula



Originally found in citrus fruits and later in animal organs and many foods, it is now manufactured synthetically from certain sugars. It was the first of the vitamins to be prepared from laboratory reagents and is also one of the simplest in structure. The outstanding properties of ascorbic acid are the dextrorotation, the solubility in water and alcohol, the acidity to litmus, and the easy oxidizability. The sodium salt and ferrous salt have been used in medicine.

OTHER OXYGENATED ACIDS

Glyoxylic acid, CHO—COOH, is found in unripe fruits and may be prepared by the oxidation of ethylene glycol, glyoxal, or glycollic acid.

Glycuronic acid, CHO—(CHOH)₄—COOH, one of several isomers with this formula because of the four asymmetric carbons, is important as a detoxifying agent in animal metabolism; camphor, borneol, chloral, phenol, and other poisons are combined with it before elimination. It seems to be a constituent part of the glycyrrhizin of licorice.

A few ketonic compounds that might be mentioned are: acetol, CH₃—CO—CH₂OH; acetylacetone, CH₃—CO—CH₂—CO—CH₃; acetonylacetone, CH₃—CO—CH₂—CH₂—CO—CH₃, used to synthesize derivatives

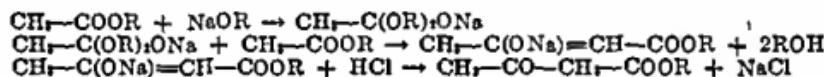
of furan and pyrrole; methylglyoxal, CH_3COCHO ; and diacetone, $\text{CH}_3\text{COCH}_2\text{CHOH(CH}_3)_2$, a commercial solvent.

The ketonic acids represent an interesting series of compounds, especially acetoacetic acid and its ester. The simplest alpha-ketonic acid, CH_3COCOOH , is called pyruvic or pyroracemic acid. It can be made in several ways, one by beating racemic acid, but most easily in industry by oxidation of propylene glycol. Levulinic acid, $\text{CH}_3\text{COCH}_2\text{CH}_2\text{COOH}$, a gamma-ketonic compound, is made by boiling starch, cellulose, sugars, or gums with dilute sulfuric acid. It is used in cotton printing. Calcium Levulinate N.R. is designed for convenience in administration of calcium.

Acetoacetic acid, $\text{CH}_3\text{COCH}_2\text{COOH}$, a beta-ketonic acid, is one of the acetonic bodies in diabetic urine. When warmed it easily loses carbon dioxide and becomes acetone, an explanation for presence of the latter in the urine and breath of diabetics. This easy loss of carbon dioxide is typical of beta-ketonic acids generally. Another characteristic of them is a tautomerism by wandering of an atom of hydrogen to form an enol.



The ethyl ester of this acid is a very useful means of synthesis, as has been indicated several times previously. It is a clear, colorless liquid with a pleasant, fruity odor and boiling at 181° . It is produced by the Claisen reaction (general for many similar esters) from ethyl acetate by means of sodium ethylate. The reactions may be quite complex, but the main results can be represented as follows:



This ester has two significant and useful properties. In the first place, it consists of two tautomeric compounds in equilibrium.

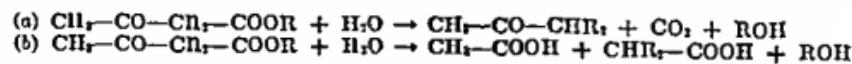


The enol form, which is present in the larger amount, gives a salt with metallic sodium or sodium ethylate, and this salt can react with halogen compounds to introduce any one of a great variety of radicals into the ester; the radical goes in as if to the methylene group of the ketone formula. Thus, with ethyl chloride



The other hydrogen atom may now be replaced by sodium and again by another radical to give compounds of the type, $\text{CH}_3\text{CO}-\text{CR}_2-\text{COOR}$.

The other property of acetoacetic ester is shared by the compounds formed through sodium and halides as just described. When hydrolyzed by alkalies, they decompose in one of two ways according to conditions to give (a) ketones or (b) acids.



With dilute alkali (a) predominates, while the main product with concentrated alcoholic alkali is according to (b), as also with fairly strong

solutions of hydrochloric or sulfuric acid. - It is thus possible to make almost any acid and many ketones simply by introducing the right radical into the ester.

REVIEW QUESTIONS

1. How can hydroxy-acids be obtained from glycols? from aldehydo- or keto-acids? from unsaturated acids? from halogen acids? from amino acids? Write equations.
2. Illustrate the dehydration of alpha, beta, and gamma hydroxy acids, using equations.
3. What two things can happen to hydroxy-acids on oxidation? Illustrate both.
4. Show by equations the action of phosphorus pentachloride and of hydrogen iodide.
5. What is a lactone? Which of this series give them? Write an illustrative equation.
6. Write formulas of glycollic acid, alpha-lactic acid, hydrarylic acid, gamma-hydroxybutyric acid, calcium gluconate.
7. Why are there three alpha-lactic acids? Name them. Which one is official? How is it made?
8. □□
9. □□
10. □□
important properties has it?
11. Write the formulas of glycuronic acid, and of glyoxylic acid.
12. How is acetoacetic ester made? Show how it illustrates tautomerism.
13. How can radicals be introduced into the molecule? Write equations.
14. In what two ways do derivatives of the ester hydrolyze? How are these brought about? Write equations.
15. Write formulas of alpha, beta, and gamma keto-acids.

CHAPTER XV

DIBASIC ACIDS

THE important compounds containing two carboxyl groups and no other substituents are of the type, HOOC—(CH₂)_n—COOH, and their alkyl substitution products. This series of homologues is headed by oxalic acid, HOOC—COOH, and is usually referred to as the oxalic series. Most of the members that we need to consider have been given common, arbitrary names, but they also may be designated according to the Geneva system, using the ending -dioic acid. Thus HOOC—CH₂—COOH is malonic acid or propanedioic acid.

The compounds of the oxalic series are crystalline solids that are soluble in water and alcohol but insoluble in ether. The lower ones are fairly strong acids but become weaker as the molecular weight increases; those containing up to five atoms of carbon are all stronger than acetic acid.

Preparation.—The methods that are used are the common ones for making acids but modified to produce two carboxyl groups: (1) Oxidation of diprimary alcohols, primary hydroxy-aldehydes, or dialdehydes. (2) Oxidation of primary hydroxy-acids and of many complicated compounds. (3) Hydrolysis of dianhydrides or diamides. (4) The malonic ester or acetone-ester synthesis.

Reactions.—The dibasic acids have the properties of the monobasic but in double the degree. Thus, they furnish normal and acid salts and two classes of esters, amides, and chlorides. In two respects they differ, however, from acids of the acetic series. Dehydration of the latter gives rise to anhydrides between two molecules, while the dibasic acids may form anhydrides within a single molecule, decompose altogether, or lose carbon dioxide. Oxalic forms carbon monoxide, carbon dioxide, and water; the second member loses carbon dioxide to form acetic acid; the third and fourth form inner anhydrides; other members form unstable anhydrides or decompose to give carbon dioxide and members of the acetic series. The tendency to lose carbon dioxide is much greater than in other series of acids, especially when the two carboxyl groups are very close together.

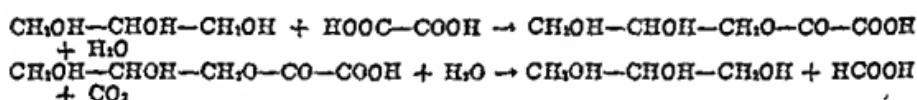
Oxalic acid, HOOCCOOH·2H₂O (ethanedioic acid), is listed as reagent and volumetric solution in the Pharmacopœia. It occurs free in some plants and as salts of sodium, potassium, or calcium in many others, such as wood sorrel (*oxalis*), rhubarb, and *rutaceæ*. The hydrated acid is a crystalline solid that is soluble in water, less so in alcohol, and insoluble in ether. It effloresces slowly in air and becomes anhydrous at 100°. At 150° to 160° it partly sublimes and partly decomposes. Its strength lies between that of dichloro- and trichloroacetic acid, dissociation constant 9×10^{-5} .

The acid is formed as an oxidation product of many natural and synthetic substances. Among these may be mentioned glycol, glyoxal, glycollic acid, sugars, starch, oils, cellulose, and gums. Although it itself is fairly easily oxidized by potassium permanganate or other agents, nitric acid has no such effect and so is the agent usually used to make it from such substances.

as ordinary cane sugar, the common laboratory method. In commerce it was formerly produced by heating sawdust with soda lye at about 250° C., and many other substances could have been employed in place of the sawdust. It is often prepared commercially today by rapidly heating sodium formate to a high temperature in the presence of carbonates or other salts; the resulting sodium oxalate is later decomposed by mineral acids. It may also be synthesized by heating carbon dioxide with sodium at 350° to 370° or by hydrolyzing cyanogen, (CN)₂.

Separation of the acid from its salts is rendered more difficult because of its insolubility in ether and other immiscible solvents. In the case of many other acids, it is routine to acidify an aqueous solution of the salt and extract the acid by means of ether. Where the acid is volatile it may be distilled in place of being extracted. Since oxalic acid is neither volatile nor soluble in ether, these two methods are not satisfactory. The method adopted is to precipitate as the calcium salt, decompose this with the theoretical quantity of dilute sulfuric acid, and evaporate the filtrate to crystallization.

Heated alone, oxalic acid partly sublimes at 150° to 160° and partly decomposes to a mixture of carbon dioxide, formic acid, carbon monoxide, and water. If it is heated with glycerin, the mono-ester that is first formed decomposes almost quantitatively to glycerin, carbon dioxide, and formic acid, a convenient method for preparing the last, essentially by loss of carbon dioxide from oxalic acid.



The reaction is much more complicated than indicated by the equations given, but the essential result is decomposition of the oxalic acid in the presence of glycerin.

With concentrated sulfuric acid, oxalic acid decomposes to water, carbon dioxide, and carbon monoxide. If the resulting gas is passed through a solution of alkali to absorb the dioxide, the monoxide may be obtained in the fairly pure state.

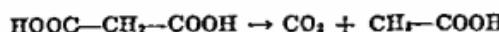
Towards chlorine or nitric acid oxalic acid is stable, but acidified potassium permanganate oxidizes it to carbonic acid, a reaction which is often used in volumetric analysis.

Like the other dibasic acids, it forms two classes of derivatives, such as salts, esters, chlorides, and amides. The mono-esters are called alkyl oxalic acids, the monamide is oxamic acid, NH₂-CO-COOH, and the diamide is called oxamide, NH₂-CO-CO-NH₂.

Oxalic acid is employed in dyeing as a mordant, in the manufacture of dyes, as an ink erector, as a metal polish, as a bleaching agent, in tanning, and in many other ways.

The sodium, potassium, ammonium and lithium salts are official reagents, while the potassium salt is used with the iron salt in photography. Potassium binoxalate, HOOC-COOK, is known also as salt of lemon or sorrel. It crystallizes with the acid to form potassium quadroxalate (tetroxalate), HOOC-COOK.HOOC-COOH.2H₂O. Cerium Oxalate N.F. is a mixture of oxalates of the rare earths, used in medicine like bismuth subnitrate.

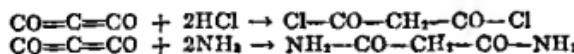
Malonic acid, HOOC—CH₂—COOH, propanedioic acid, occurs in beet root as the calcium salt, and probably in other plants. It is crystalline, soluble in water and alcohol, and melts at 132°. It is much weaker than oxalic, dissociation constant 1.6×10^{-3} . Heated somewhat above its melting point, it decomposes to carbon dioxide and acetic acid.



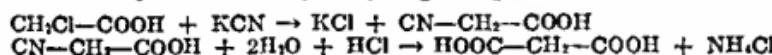
About 10 per cent, however, is converted to carbon suboxide by loss of 2 molecules of water, and the amount of this can be increased by adding a strong agent like phosphorus pentoxide.



This oxide is an unstable, poisonous gas which unites with water to reverse the reaction of formation, with hydrogen chloride to form the chloride of malonic acid, and with ammonia to form the amide.



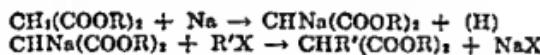
Malonic acid is usually prepared from monochloroacetic acid by heating with a metallic cyanide and hydrolyzing the product.



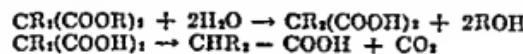
It may be made by oxidation of malic acid, the source of its name, and by hydrolysis of its derivatives, as the ethyl ester of malonylurea.

Ethyl or methyl malonate, known collectively as malonic ester, is of great importance in industry and in the laboratory for the synthesis of numerous compounds. It can be manufactured by direct esterification of the acid or by heating cyanacetic acid with the dehydrated alcohol in the presence of hydrogen chloride. Both esters are pleasantly aromatic liquids, the ethyl compound boiling at 198° and the methyl at 181°.

The usefulness of malonic ester rests upon replaceability of the methylene hydrogens and easy loss of carbon dioxide from derivatives of malonic acid. The substitution in the ester of sodium for the hydrogen and subsequent introduction of radicals for sodium goes on in the same manner and for the same reason as in acetoacetic ester.



Another radical may be substituted for the second hydrogen in the same way. Finally the derived ester so prepared is hydrolyzed and heated, giving carbon dioxide and a new acid.



By suitable selection of the substituent, many esters can be made by this method.

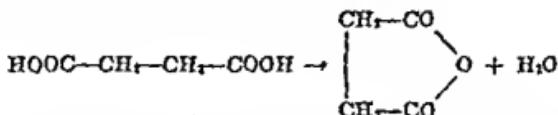
Thus, the reaction of malonate with sodium malonate gives diethyl malonate, and subsequent hydrolysis and heating gives HOOC—CH₂—CH₂—CH₂—COOH, a member of the oxalic series.

Succinic acid, HOOC—CH₂—CH₂—COOH, butanedioic acid, melts at 185° and can be boiled at 235° with partial dehydration. It occurs in unripe grapes, urine, blood, and other natural materials, and it can be formed in various fermentations and by distilling amber, resins, fossil

wood, or lignites. Its name is from "succinum" meaning amber. It can also be made by oxidation of fats or paraffins by hot nitric acid.

Synthetically succinic acid can be prepared in several ways: from ethylene chloride or bromide through the cyanide; from beta-bromopropionic acid through the cyanide; by electrolytic reduction of maleic or fumaric acid; from malonic ester. The last is carried out with the aid of bromoacetic ester as the halide; as an exercise the student should write equations for the reactions involved. Recently it has been found most economical to prepare the acid by the reduction of maleic acid, which has become a cheap article of commerce because of easy formation by catalytic oxidation of benzene.

The acid can be converted into an anhydride by heating, with or without acetic anhydride or phosphoryl chloride, POCl_3 .



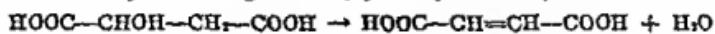
This is a solid melting at 120° and boiling undecomposed. Water slowly reconverts it to the acid, while alcohol acts upon it to form an acid ester, and ammonia forms an imide. (See Chapter XVII.)

Ethyl succinate is a solvent for fruit flavors, and benzyl succinate has been employed in medicine to relax muscular spasms.

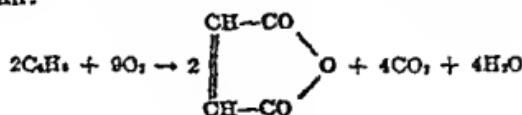
Glutaric acid, $\text{HOOC}-(\text{CH}_2)_3-\text{COOH}$, found in wool and in beet root, can be prepared by the action of formaldehyde on malonic ester or of methylene bromide on sodium malonic ester. It forms an anhydride and imide as does succinic acid.

Other acids of the series are of minor importance but will occasionally be encountered. Isosuccinic acid or methylmalonic acid, $\text{CH}_3-\text{CH}(\text{COOH})_2$, is most easily made from malonic ester, and forms no anhydride. Methylsuccinic acid or pyrotartaric acid, $\text{HOOC}-\text{CH}(\text{CH}_3)-\text{CH}_2-\text{COOH}$, is one of the products of heating tartaric acid and can be prepared by heating pyruvic acid with hydrogen chloride. Adipic acid, $\text{HOOC}-(\text{CH}_2)_6-\text{COOH}$, is often an oxidation product of animal and vegetable matter, most easily by the action of nitric acid on fat. Others of the series are pimelic, suberic, azelaic, and sebacic, with five, six, seven, and eight methylene groups respectively.

Maleic and fumaric acids are geometric isomers of the formula $\text{HOOC}-\text{CH}=\text{CH}-\text{COOH}$. Fumaric, the trans form, is found in several fungi, in Iceland moss, and in other plants, but maleic is not found in nature. Both can be obtained by distilling malic (hydroxysuccinic) acid.



The anhydride of maleic acid distils and fumaric acid is left as a residue; at 140° to 150° the chief product is the latter, but if the heating is bigger and rapid, it is mostly converted to the volatile anhydride. Recently it has been found more economical to produce this by the catalytic oxidation of benzene in air.



These acids reduce readily to succinic, hydrate to malic, and oxidize with dilute permanganate to tartaric acid. The anhydride will condense with conjugated diolefins, such as furane or cyclopentadiene, a very useful reaction in synthesis (Diehl and Alder) which will be mentioned again.

Other unsaturated dibasic acids that might be noted are: pyrocinchonic acid, known in the form of its anhydride, dimethylmaleic anhydride; and itaconic acid, HOOC—C(=CH₂)—CH₂—COOH, obtained by heating citric acid.

REVIEW QUESTIONS

1. State four methods for making dibasic acids and write equations to illustrate.
2. Write formulas of oxalic, malonic, succinic, and glutaric acids.
3. What is the effect of heat or dehydration on each? Write equations.
4. How is oxalic acid produced in the laboratory? commercially?
5. What is the effect of dehydrating agents on it? of heating with glycerin? of oxidizing agents? Write equations.
6. What salts are used as reagents? in photography? in medicine?
7. What are salt of sorrel, salt of lemon, potassium binoxalate, potassium quadroxalate, oxamic acid, oxamide, methylxallic acid?
8. How is the acid obtained from its salts?
9. How is malonic acid made? Write equations.
10. Write equations to show how the ester is used in preparing other acids.
11. Write formulas of succinic anhydride, carbon suboxide, pyrocinchonic anhydride, itaconic acid.
12. Name and give the formulas of two other acids of this series.
13. What is the relation of maleic and fumaric acids? Explain. What is the cis form?
14. How can they be made from malic acid?
15. How is technical maleic anhydride made from benzene?
16. In what way is it used in synthesis?

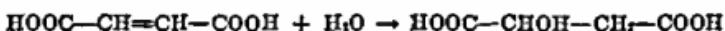
CHAPTER XVI

HYDROXY-POLYBASIC ACIDS

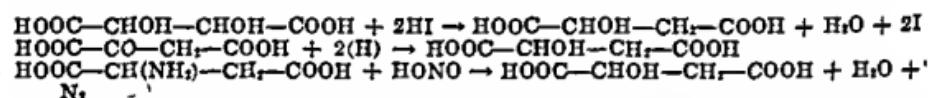
THE simplest of these is tartronic acid, HOOC—CHOH—COOH, or hydroxymalonic acid. It is obtained by the action of potassium permanganate, from its salt with potassium hydroxide, on the product, and by reduction of malic acid with sodium amalgam. It is easily soluble in water, alcohol, or ether, and decomposes when heated above the melting point to carbon dioxide and glycolic acid.

Malic acid, HOOC—CHOH—CH₂—COOH, or hydroxysuccinic acid, occurs very widely in the vegetable kingdom, mostly in unripe fruits as gooseberries, cherries, apples, sorb apples, grape, and quince. Its name is derived from the Latin *malum* meaning apple. The natural levo acid crystallizes in needles that melt at 100° and are soluble in water or alcohol but sparingly so in ether. The racemic compound as synthetically manufactured melts at 130° to 131°.

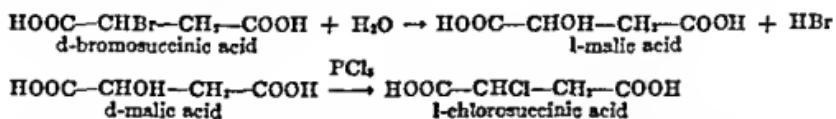
The commercial method for preparing it is from fumaric or maleic acid which is hydrated in the presence of potassium hydroxide or sulfuric acid.



It can be made by reducing tartaric acid with hydrogen iodide or oxalic acid with sodium amalgam, or by treatment of aspartic acid with nitrites in acid solution.

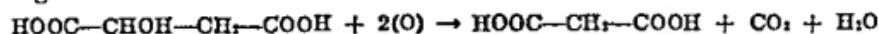


The most interesting synthesis is from succinic acid. Bromination of this optically inactive compound gives a monobrom derivative containing an unsymmetric carbon atom but racemic as made. If this is resolved into its isomeric levo and dextro components and each is converted to malic acid by hydrolysis, the product has the opposite sign; d-bromosuccinic acid yields l-malic acid, and the levo bromine compound forms d-malic acid. This change in direction of optical rotation by chemical transformation is but another instance of the Wnlden inversion that has been mentioned before and will be encountered frequently. If now the native malic acid is converted to chlorosuccinic acid by means of phosphorus pentachloride, the sign is again changed.



Malic acid can be reduced to succinic acid by hydriodic acid or by certain fermentative processes. As was noted earlier, heating above 140° converts it by dehydration into fumaric acid and maleic anhydride. Oxidation by permanganate or hydrogen peroxide in the presence of ferrous

salts changes it to oxalaetic acid, HOOC—CO—CH₂—COOH, but chromic acid gives malonic acid and carbon dioxide.



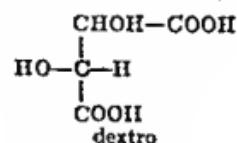
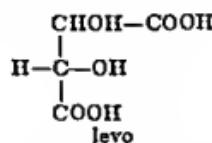
Malic acid furnishes mono and di chlorides and correspondingly two kinds of esters and amides.

Since the development of cheap methods for making maleic acid from benzene and the easy hydration of this to malic acid, the latter has become quite widely used in industry, especially in the preparation of fruit preserves, candies, and effervescent salts. Sodium malate is sometimes used as a substitute for sodium chloride when a salt-free diet is necessary.

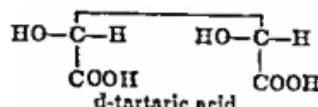
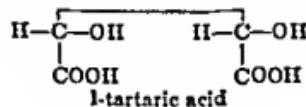
Hydroxy derivatives of other members of the oxalic series are known but of less importance. For example, alpha-hydroxyglutaric acid, HOOC—CHOH—CH₂—CH₂—COOH, is found in molasses and is probably of wide occurrence because of its close relationship to glutamic acid, the corresponding amino compound and one of important amino acids from proteins.

Tartaric acid, HOOC—CHOH—CHOH—COOH, dihydroxysuccinic acid, contains two asymmetric atoms of carbon, both of which are alike in the substituting radicals. For each of these it is possible to have dextro and levo configurations. If the substituents in each are arranged so that both exert dextro rotation, then the compound will be dextro; conversely if both are levo, then the compound will be levo. On the other hand, if the arrangement of radicals in each is such that the effects within the molecule oppose each other, then the compound will be inactive because each carbon is linked to the same kinds of radicals and must be quantitatively like the other in rotation. A compound with such a configuration is called meso and is entirely different from the racemic mixture of dextro and levo modifications. A meso form is only possible when a compound contains two asymmetric atoms of carbon, each connected to the same kinds of radicals as the other.

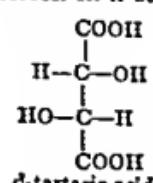
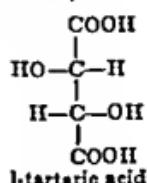
Representations of the four forms of tartaric acid can easily be made with the models and this should be done. If we think of the arrangement around 1 atom of carbon, with hydrogen on one side and hydroxyl on the other to stand for levo, and the reverse structure for dextro, we have



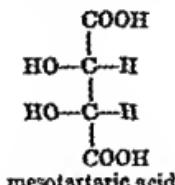
If we do the same for the second atom of carbon and connect the two to give the tartaric acids, these would be



The formulas, however, would usually be written in a straight line as



The racemic compound would be a mixture of these, but the meso could be represented as



where the influence of the 2 carbon atoms is exerted in opposite directions.

Dextrotartaric acid is widely distributed in the vegetable kingdom, being quite abundant in several fruits and especially the grape. After fermentation of grape juice in making wine, potassium bitartrate deposits in the casks as argol or argols. From this the acid may be obtained by precipitating with a calcium salt and decomposing the calcium tartrate by sulfuric or oxalic acid. Tartaric Acid U.S.P. is usually the dextro form, although the Pharmacopoeia does not specify which one is to be used and presumably any of them would be acceptable. The acid is a colorless, crystalline solid melting at 163° to 170°, soluble in water or alcohol but not in ether. The levo acid is quite similar in general properties.

Tartaric acid can be reduced by hydrogen iodide to malic acid and finally to succinic acid. Oxidation converts it into a variety of substances, depending upon the agent used and other conditions. Among these may be mentioned tartronic, dihydroxyfumaric, carbonic, and formic acids. When heated with water to about 160°, it gradually changes to the meso form, but at higher temperatures gives the racemic. Dry distillation of the acid yields pyroracemic or pyruvic acid, $\text{CH}_3-\text{CO}-\text{COOH}$, and pyrotartaric acid, $\text{CH}_3-\text{CH}(\text{COOH})-\text{CH}_3-\text{COOH}$.

The salts of tartaric acid are frequently employed in medicine and industry. The most important of these are the official ones and those described as reagents. Potassium Bitartrate U.S.P. (Cream of Tartar), $\text{HOOC}-\text{CHOH}-\text{CHOH}-\text{COOK}$, is difficultly soluble in water. Hence, it can be precipitated when a potassium salt in not too dilute solution is treated with tartaric acid or when a solution of the normal tartrate is acidified with acetic acid. The analogous sodium bitartrate and also sodium tartrate are used as reagents.

Potassium and Sodium Tartrate U.S.P. (Rochelle Salt), $\text{NaOOC}-\text{CHOH}-\text{CHOH}-\text{COOK} \cdot 4\text{H}_2\text{O}$, is formed when cream of tartar is neutralized by sodium hydroxide. It is an ingredient, together with tartric acid and sodium bicarbonate, of Compound Effervescent Powder U.S.P. (Seidlitz Powder).

Antimony and Potassium Tartrate U.S.P. (Antimonyl Potassium Tartrate, Tartrated Antimony, Tartar Emetic), $\text{KOOC}-\text{CHOH}-\text{CHOH}-\text{COO}-(\text{SbO}) \cdot 1/2\text{H}_2\text{O}$, is used in medicine and in the dyeing industry. The analogous Bismuth and Potassium Tartrate U.S.P. and Bismuth Sodium Tartrate N.R. are used in the treatment of syphilis.

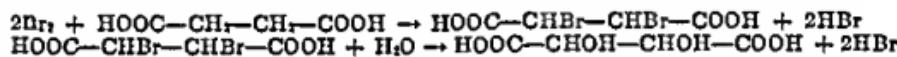
Presence of the two hydroxyl groups makes it possible to form alcoholates, even with metallic hydroxides because of the proximate carboxyls. Thus, the acid can behave as a tetrabasic compound and apparently does so in the tartrate scale salts of iron, in Bismuth Sodium Potassium Tartrate N.R. (Bismosol), and in the much used Fehling's solution or alkaline

cupric tartrate test solution. In this reagent a solution of copper sulfate (Fehling's solution No. 1) is mixed, when about to be used, with a solution of Rochelle salt and sodium hydroxide (Fehling's solution No. 2). The usual precipitate of cupric hydroxide does not appear because it reacts with the tartrate to give a dark-blue solution containing potassium sodium cupric tartrate, $\text{NaOOC}-\text{CH}(\text{O})-\text{CH}(\text{O})-\text{COOK}$. Reducing agents, such



as aldehydes, sugars, etc., change the valence of copper to 1, and there results a yellow precipitate of cuprous hydroxide that quickly dehydrates to red cuprous oxide.

Racemic acid (para tartaric acid, dl-tartaric acid) consists of efflorescent, rhombic crystals that contain 2 molecules of water and melt at 205° to 206° when anhydrous. While it occurs in nature with the dextro form, it is best prepared by one of several methods. It is formed by the oxidation of mannitol, dulcitol, or similar alcohol by nitric acid, or of fumaric or piperic acid by permanganate. Among the usual laboratory methods might be mentioned: (1) from succinic acid by bromination and subsequent treatment of the product with moist silver oxide;



and (2) from glyoxal through addition of hydrogen cyanide.



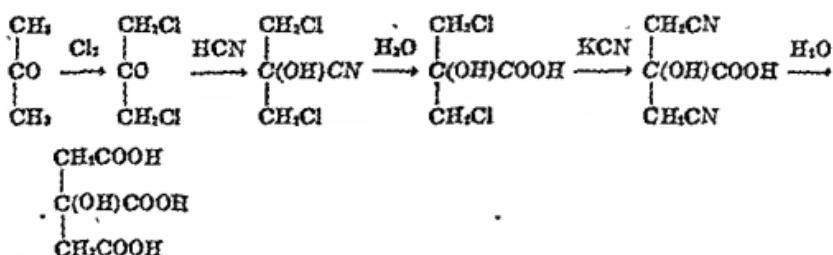
Resolution of the acid into ordinary tartaric acid and its levo isomer can be readily accomplished by crystallization of the cinchonine or quinine salts, because of differences in solubility. It can be done mechanically, as by Pasteur, by converting into sodium ammonium salt and picking out the two kinds of crystals that are mirror images of each other. Preparation of l-tartaric acid from the racemic can be performed by submitting to the action of *Penicillium glaucum* which destroys the dextro compound.

Mesotartaric acid crystallizes with 1 molecule of water in rectangular, efflorescent plates, melting at 143° . It is most readily prepared by heating the dextro compound with water at about 160° for a day or so. Other methods of manufacture in the laboratory include oxidation of sorbitol by nitric acid or of maleic anhydride by permanganate. It can be converted to racemic acid by heating with water to about 175° . Potassium acid mesotartrate is quite soluble as contrasted with the difficultly soluble cream of tartar.

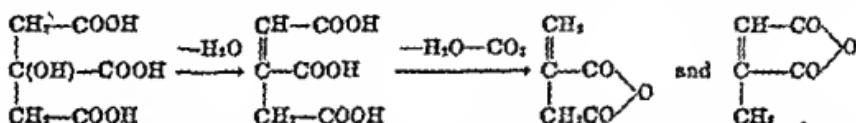
Citric Acid U.S.P., $\text{HOOC}-\text{CH}_2-\text{COH}(\text{COOH})-\text{CH}_2-\text{COOH}\cdot\text{H}_2\text{O}$, occurs in many plants, mainly in the form of calcium and other salts, but often free in fruits such as cranberries, gooseberries, currants, oranges, lemons, and grapefruit. It crystallizes in large prisms that lose their water at about 100° and then melt at 153° . It is soluble in water or alcohol but difficultly so in ether.

Formerly the compound was prepared entirely from lemon juice (6 to 7 per cent) by precipitation as calcium salt and liberating from the latter by addition of mineral acids. Today much of the supply is obtained by fermentation of dextrose or sucrose through the mediation of certain kinds

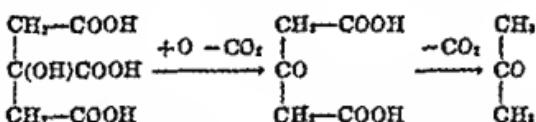
of molds, *Citromyces glaber* or *Aspergillus niger*. From acetone it can be synthesized by the changes indicated in the diagram:



Citric acid loses water at about 175° to form aconitic and, by rapid beating, itaconic and citraconic anhydrides.



At the same time a portion is converted to acetone dicarboxylic acid by oxidation and loss of carbon dioxide, and this in turn gives acetone by loss of carbon dioxide.



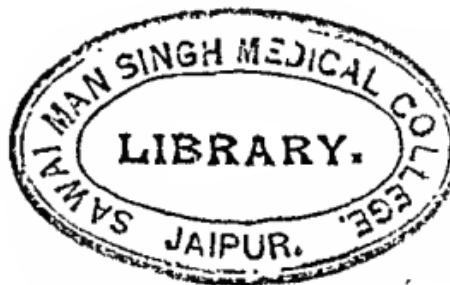
Oxidation by nitric acid or fusion with caustic potash gives acetic and oxalic acids. Reduction with hydrogen iodide forms tricarballylic acid, $\text{HOOC---CH}_2\text{---CH(COOH)}\text{---CH}_2\text{---COOH}$, a compound that occurs in unripe beets.

The citrates are of several types because there are 3 replaceable atoms of hydrogen, one of which differs from the others in position, and because the hydroxyl group may also form salts. Among the normal tertiary salts used in medicine are: Sodium Citrate U.S.P. which crystallizes with 2 molecules of water and is very soluble; Potassium Citrate U.S.P., crystallizing with 1 molecule of water and still more soluble; Lithium Citrate N.F., a deliquescent, soluble salt; and Copper Citrate N.N.R., a bluish-green, insoluble powder. Solution of Magnesium Citrate U.S.P., made by dissolving magnesium carbonate in a solution of citric acid, probably contains a mixture of normal and acid salts. Insoluble compounds of iron or manganese can be dissolved by solutions of the alkali or ammonium citrates, the explanation probably being similar to that for the corresponding tartrates. The heavy metals are in this way masked, since they cannot be precipitated from the solutions by the usual reagents such as ammonia water. Evaporation of the solutions on a plate produces a varnish-like resin that can be broken up to pieces or scales. Among these scale salts are Iron and Ammonium Citrates U.S.P., Green Iron and Ammonium Citrates U.S.P., Soluble Ferric Phosphate N.F., Soluble Ferric Pyrophosphate N.F., and Soluble Manganese Citrate N.F. Tincture of Ferric Citrochloride N.F. probably contains a similar solution of ferric citrate. Tartrate scale salts of iron are similar to these.

Saccharic acid, HOOC—(CHOH)₄—COOH, can be obtained by oxidation of dextrose, sucrose, starch, and other carbohydrates by nitric acid. It is a syrupy, deliquescent substance that easily changes to a crystalline lactone by loss of water. Four of the carbon atoms are asymmetric, so that there are 9 other compounds with the same formula. Of these mucic acid and mannosaccharic acid are the only important ones. The latter is obtained from mannonic acid by oxidation and the former from galactose, lactose, or dulcitol by the same means.

REVIEW QUESTIONS

1. Write formulas of tartaric, malic, and tartaric acids and name as derivatives of malonic and succinic acids.
 2. What two compounds are formed by heating malic acid? Write equation.
 3. What is meant by the Walden inversion? Illustrate.
 4. Name the four tartaric acids Which is the common one? Which are official? Write formulas of all four.
 5. Write equations to show progressive reduction of tartaric acid by hydrogen iodide.
 6. Which of the tartrates are official?
 7. What are argol, cream of tartar, Rochelle salt, Seidlitz powder, tartar emetic, racemic acid, paratartaric acid, Fehling's solution, mesotartaric acid, and Bismosol?
 8. How can racemic acid be resolved?
 9. Write the formula of citric acid. What is the chief natural source? How is it made from sugars?
 - 10.
 - 11.
 - 12.
- from citric acid? Write equations
13. Which of the citrates are official? What are scale salts and how are they made? Name three official ones.
 14. Write the formulas of saccharic and mucic acids. How is each prepared?
 15. Name each of the acids mentioned in this chapter by the Geneva system.



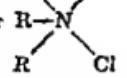
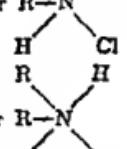
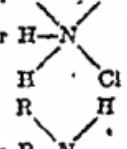
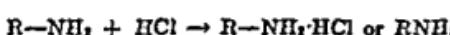
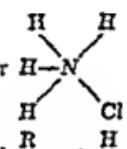
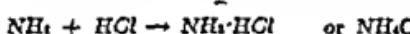
CHAPTER XVII

AMINES

THE amines are derived by substitution of alkyl for the hydrogen of ammonia, ammonium hydroxide, or ammonium salts. From the first we get $R-NH_2$, primary; R_2NH , secondary; and R_3N , tertiary. The student should note carefully that the terms primary, secondary, and tertiary are here used in a different sense than in the alcohols; the criterion is the number of alkyls substituted for hydrogen of ammonia.

From ammonium hydroxide are obtained the amine bases. Just as ammonia in aqueous solution is presumed to give ammonium hydroxide, so the amines in similar solution probably produce substituted ammonium hydroxides which ionize in the same way to give hydroxyl ions. General formulas for these are RNH_3OH , primary; R_2NH_2OH , secondary; and R_3NOH , tertiary.

Analogous to ammonium salts are compounds formed by simple addition of acids, just as ammonia adds these same acids.



Finally, we also have the quaternary ammonium salts, such as R_4NCl or $(R_4N)_2SO_4$, and the corresponding quaternary ammonium bases, R_4NOH . In all of these formulas so far given the student must bear in mind that, when more than one alkyl radical is given, these may be alike or different. Thus there are eleven types of amines, their salts, and their bases, all perfectly analogous to ammonia and its compounds. There are three primary, three secondary, three tertiary, and two quaternary.

Nomenclature.—The simple compounds are named as alkyl derivatives of ammonia (amine), while the others are alkylammonium salts or hydroxides. In the following list are given the methyl derivatives and chlorides as illustrations of the eleven types.

Primary

$R-NH_2$	CH_3-NH_2	methylamine
$R-NH_2Cl$	CH_3NH_2Cl	methylammonium chloride
$R-NH_2OH$	CH_3NH_2OH	methylammonium hydroxide

Secondary

R_2NH	$(CH_3)_2NH$	dimethylamine
R_2NHCl	$(CH_3)_2NHCl$	dimethylammonium chloride
$R_2NH\cdot OH$	$(CH_3)_2NH\cdot OH$	dimethylammonium hydroxide

Tertiary

R_3N	$(CH_3)_3N$	trimethylamine
R_3NCl	$(CH_3)_3NCl$	trimethylammonium chloride
R_3NOH	$(CH_3)_3NOH$	trimethylammonium hydroxide

Quaternary

R_4NCl	$(CH_3)_4NCl$	tetramethylammonium chloride
R_4NOH	$(CH_3)_4NOH$	tetramethylammonium hydroxide

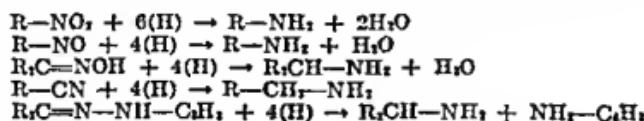
In more complicated amines the salts are often also designated as hydrochlorides of the particular compound, or as sulfates or nitrates and in general similarly for other acids added. Thus, $(CH_3)_2NH_2Cl$ would be dimethylamine hydrochloride and is then written $(CH_3)_2NH \cdot HCl$.

In the Geneva system the primary group $-NH_2$ is expressed by the prefix amino-, using the appropriate number. The simple alkyl derivatives (secondary and tertiary) are called alkylamino substitution products, such as methylamino- or diethylamino-. Thus, the compound $CH_3-CH_2-CH_2-CH_2-NH_2$ is *n*-butylamine or 1-aminobutane, while $CH_3-CH_2-CH_2-CH(CH_2OH)-NH-CH_3$ is 2-methylaminopentanol.

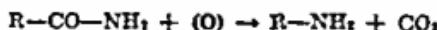
Physical Properties.—All of these compounds with the exception of some salts are colorless, the lower ones being gases and the higher ones liquids and solids. The quaternary salts, as also other salts, are crystalline solids, while the quaternary bases (hydroxides) are usually very hygroscopic solids. In general all of the compounds dissolve readily in water and alcohol, although those containing trivalent nitrogen and a high molecular weight are difficultly soluble in water or insoluble. The specific gravity of the simple amines is always less than 1. The lower amines have an ammoniacal odor, sometimes with added fishy character. They are unlike ammonia in being readily combustible. Many of them form oily, hygroscopic, unstable hydrates which are analogous to the hypothetical ammonium hydroxide.

Preparation.—1. All classes may be made by alkylation which will be explained fully under the reactions.

2. Primary amines, and sometimes secondary, can be obtained by reduction of other nitrogenous compounds, such as nitro or nitroso compounds, oximes, cyanides, isocyanides, or phenylhydrazones.

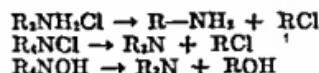


3. The Hofmann degradation of an amide by means of alkaline hypobromite gives a primary amine. This will be discussed in greater detail under reactions of the amides, but it may be represented here by the equation

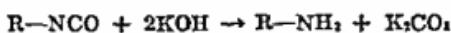


4. All three classes of simple amines may be produced by dry distillation of amine salts or of quaternary bases. These reactions may be used

for commercial production of alkyl halides or hydroxides as well as of the amines.

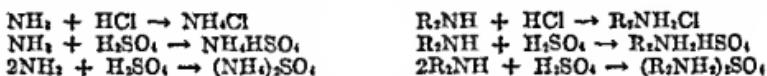


5. Distillation of an isocyanate with potassium hydroxide yields a primary amine.



Other methods for making all classes of amines will be noted from time to time. The first four given are most often used and should be well studied.

Reactions.—1. Solutions of the lower amines are stronger bases than ammonia and often show higher basicity as the number of alkyl groups increases. The quaternary bases are on a par with the caustic alkalies and will absorb carbon dioxide to produce carbonates. Like ammonia, the simple amines fume with volatile acids and neutralize acids to form the salts.



The basic properties in aqueous solution are shown by ability to precipitate metallic hydroxides and to redissolve many of them when in excess.

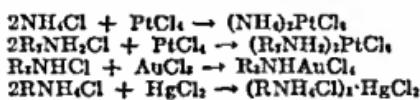


Unlike ammonium hydroxide, they do not redissolve the hydroxides of nickel and cobalt.

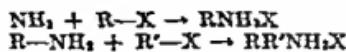
The salts formed by addition of acids are crystalline solids which are generally soluble in alcohol or water and are highly ionized. From these salts the base may be liberated by addition of alkalies. The quaternary salts, however, are not so altered because the bases are as strong as the reagents. In this case the free base may be produced readily by action of moist silver oxide because of the insoluble silver salt that is formed.



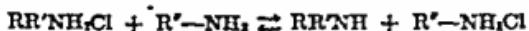
All of the salts can combine, as do those of ammonium, with some metallic salts to give double compounds. Some of these, as will be noted later, can be used for identification or estimation of the amine.



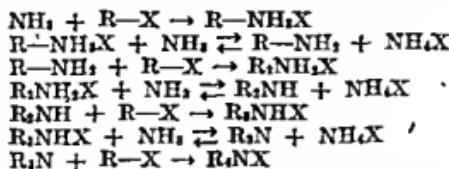
2. **Alkylation.**—When ammonia or an amine with trivalent nitrogen is heated with an alkyl halide, addition takes place to form a salt.



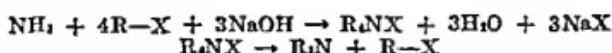
This is perfectly analogous to the formation of salts by addition of acids. The resulting compounds, if primary, secondary, or tertiary salts, will give up hydrohalogen to bases and free the amine, as we have already seen. Any excess of the original amine, which is a base, will tend to bring about this reaction, but only partly since the process must necessarily be reversible.



If we started with ammonia, therefore, we could get the following series of changes:



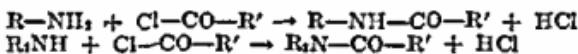
Actually the resulting product is a mixture of these various compounds, and it is difficult to separate any individual from it. On the other hand, if an alkali is added to the ammonia before starting, all of the reversible reactions proceed to the right by withdrawal of ammonium halide, and the quaternary salt is the product. Subsequent distillation of the latter can give the tertiary amine.



By careful control of conditions, it is often possible to prepare primary and secondary amines by the process; as a means for preparing the amines from ammonia or less alkylated amines, it is sometimes very useful.

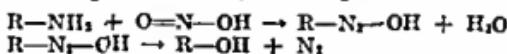
For such alkylations the halides are generally employed, but other inorganic esters are efficient. For example, the U.S.P. XI directed dimethyl sulfate for the methylation of theobromine and theophylline to caffeine in the official assays. Diethyl sulfate can likewise be used for ethylations. It is notable that tertiary halides do not alkylate but are converted to unsaturated compounds by withdrawal of hydrohalogen, just as they would be by treatment with alcoholic alkali.

3. Acylation.—Primary or secondary amines react with acylating agents (acid, anhydride, or acyl chloride) to give amide derivatives.

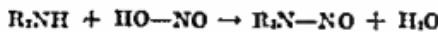


In each case, of course, the hydrogen chloride combines with excess amine to form a salt or with basic substances that have been added. Just as alcohols can be acylated to form esters, therefore, amines can be acylated to form amides; like the esters these can be easily hydrolyzed to regenerate the original amine. Acetylation, which is a special case of acylation, is frequently useful for identifying a particular amine.

4. Nitrous Acid.—The reaction of nitrous acid is an excellent means for distinguishing the three classes of simple amines. Primary compounds at room temperature condense to split out water giving diazo compounds which immediately and spontaneously decompose to alcohols and nitrogen.



Secondary amines also liberate water but in a different way, to produce nitrosoamines or nitrosamines.

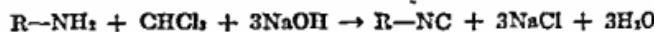


From these yellow, volatile liquids the amines can be regenerated by boiling with dilute acids. Tertiary compounds are not affected by nitrous acid except to form a salt.



The nitrous acid for these reactions is always generated in the vessel from sodium or potassium nitrite and a mineral acid, so that the salts of tertiary amines are generally with this mineral acid.

5. Carbylamine Reaction.—When primary amines are heated with chloroform and a caustic alkali, an isocyanide or carbylamine is produced. This has a characteristic, disagreeable odor and is very poisonous. The production of this odor can be used for detecting either chloroform or the primary amine.



6. Dry distillation of the salts brings about decomposition to alkyl esters and amines. As was noted under methods of preparation, this can be used as a convenient process for obtaining the amines, but it is also employed to produce alkyl halides.



Some of the lower amines are quite common because they occur in natural materials or in their products of decomposition. Methylamine arises from various putrefactions. Trimethylamine, which is a commercial article, is found in herring brine and in many flowers and can be obtained by distilling any of a variety of vegetable and animal products, such as sugar-beet residues. Ethylamine is made catalytically from ethylene and ammonia under pressure in the presence of molybdic acid.

Several amines have recently been introduced into medicine for action on muscles and vessels similar to epinephrine. Tuamine (2-aminobutane) and Octin (6-methylamino-2-methylheptene) are examples.

Ethanolamine N.N.R. is prepared by action of ammonia on ethylene oxide which was described in Chapter VIII. The viscous, hygroscopic liquid is a mixture of compounds chiefly triethanolamine, $(\text{CH}_2\text{CH}(\text{CH}_2)_2)_3\text{N}$, but also containing some of the mono and di derivatives, $\text{CH}_2\text{CH}(\text{CH}_2)_2\text{NH}_2$ and $(\text{CH}_2\text{OH}-\text{CH}_2)_2\text{NH}$ respectively. It is used in soaps, emulsions, solvents, cosmetics, depilatories, and other preparations. Alky derivatives of the ethanolamines are also commercial articles.

Choline, $\text{CH}_2\text{OH}-\text{CH}_2-\text{N}(\text{CH}_3)_3\text{OH}$, a similar quaternary base, widely found in animals and vegetables, chiefly combined into lipids lecithin. Choline chloride is an official reagent. When choline is dehydrated there is obtained the unsaturated neurine, $\text{CH}_2=\text{CH}-\text{N}(\text{CH}_3)_3\text{OH}$, a poisonous product of putrefaction. Muscarine, the toxic ingredient of mushrooms, probably has the structure, $\text{CH}_3-\text{CH}_2-\text{CHOH}-\text{CH}(\text{CHO})-\text{N}(\text{CH}_3)_3\text{OH}$, and is thus a close relative.

Derivatives of choline also occur widely in the animal and vegetable kingdoms. Acetylcholine, $\text{CH}_3-\text{CO}-\text{O}-\text{CH}_2-\text{CH}_2-\text{N}(\text{CH}_3)_3\text{OH}$, has often been isolated and is found in ergot, is formed during the transmission of nerves and is presumably the medium by which nervous impulses are transmitted. It has immense physiological activity as a parasympathomimetic stimulant, but the ease with which it is hydrolyzed to inert choline limits any extensive use. The chloride (acecoline) is an official reagent.

Acetyl- β -methylcholine, $\text{CH}_3-\text{CO}-\text{O}-\text{CH}(\text{CH}_3)-\text{CH}_2-\text{N}(\text{CH}_3)_3$, has similar action and is more stable. The salt, Mecholyl Bromide, has replaced the chloride, which is used as a reagent.

Doryl, Lentin), $\text{NH}_2-\text{CO}-\text{O}-\text{CH}_2-\text{CH}_2-\text{N}(\text{CH}_3)_2\text{OH}$, another remedy of this class, is claimed to be more effective.

Betaine Hydrochloride N.N.R., which is used in medicine as a convenient source of hydrochloric acid, is the salt of betaine, $\text{CO}-\text{CH}_2-\overset{\text{N}(\text{CH}_3)_2}{\underset{\text{O}}{|}}$.

It is often found in growing plants and gets its name from the common beet, *Beta vulgaris*.

Quaternary ammonium salts with at least one long chain have been applied as water repellants, wetting agents, and bactericides. Those most commonly used are zephiran, phenacrol, and ceeprym, all of which contain cyclic nuclei and will be described later.

Phospholipids or phosphatides, occurring so commonly in plants and animals, are fat-like substances that contain nitrogen and phosphorus. They may be regarded as fats in which one of the esterifying groups has been replaced by that of cholinephosphoric acid or a related substance. The most important compounds are lecithins which occur in egg-yolk, brain and nerve matter, soy bean, and other materials. They are white to yellowish-brown, waxy solids that are insoluble in water but swell up and form a colloidal suspension, sparingly soluble in cold alcohol, and soluble in ether and oils. Upon hydrolysis the lecithins form glycerin, fatty acids, phosphoric acid, and choline. They have never been obtained in a very pure state, and the composition of any one compound is always doubtful, but the formula may be represented as $\text{CH}_2\text{OCOR}-\text{CHOCOR}'-\text{CH}_2\text{OPO(OH)OCH}_2-\text{CH}_2-\text{N}(\text{CH}_3)_2\text{OH}$, where R and R' stand for the residual radicals of fatty acids. Lecithin, obtained commercially from egg or soy bean, is used in tanning and a small amount is added to chocolates to prevent "graying". Cephalins are similar compounds that furnish ethanolamine in place of choline.

Closely related to lecithin and cephalin are sphingomyelins and cerebrosides. The former hydrolyze to fatty acids, choline, phosphoric acid, and a base sphingosine, $\text{C}_{18}\text{H}_{33}(\text{OH})\text{NH}_2$, but do not contain glycerin. The cerebrosides furnish fatty acids and sphingosine, also a sugar, but phosphorus is lacking. Some of the fatty acids found in these compounds are unique in character but are closely related to those from fats.

POLYAMINES

Ethylenediamine, $\text{NH}_2-\text{CH}_2-\text{CH}_2-\text{NH}_2$, may be prepared by heating ethylene chloride with ammonia or by reducing cyanogen. It is a hygroscopic liquid boiling at 117° and miscible with water with which it forms a dihydrate. It is used as a solvent for a few drugs and in industrial articles. Theophylline with Ethylenediamine U.S.P. contains about 20 per cent of this substance, probably in loose combination. When the hydrochloride of ethylenediamine is heated, it loses ammonium chloride and yields the beautifully crystalline diethylene diamine, formerly often used in the treatment of rheumatism under the title of "Piperazine."



The corresponding 1,4-diaminobutane, $\text{NH}_2-(\text{CH}_2)_4\text{NH}_2$, is the so-called ptomaine, putrescine, while another of these ptomaines is cadaverine, 1,5-diaminopentane, $\text{NH}_2-(\text{CH}_2)_4\text{NH}_2$. Spermine from certain kinds of

animal sperm is a similar tetramine, $\text{NH}_2(\text{CH}_2)_3\text{NH}-(\text{CH}_2)_5\text{NH}-(\text{CH}_2)_7\text{NH}_2$.

Methenamine U.S.P. (Formin, Cystogen, Urotropin, Hexamethylleae-tetramine), $(\text{CH}_2)_6\text{N}_4$, is prepared by evaporating a mixture of ammonia water and solution of formaldehyde.



Because the addition of dilute acids will reverse this reaction to liberate formaldehyde, methenamine is used as an antiseptic, especially in the urinary tract which can be made acid. The structure of methenamine has offered a great field for investigation and speculation, but it cannot be said to have been established. The usual text-book formula is cyclic in character but is hardly consistent with the great instability toward acids. Methenamine is also employed industrially, chiefly in the production of artificial resins. Siomine N.N.R., its tetraiodide $(\text{CH}_2)_6\text{N}_4\text{I}_4$, contains about 78 per cent of iodine.

When two or more amino groups are substituted in the same carbon atom, we get distinctly different classes of compounds genetically related to the ketones, aldehydes, and acids. In each case ammonia may split out, just as does water from the corresponding carboxylic acids. Primary carbon thus gives $\text{R}-\text{NH}_2$, secondary carbon gives $\text{R}_2\text{C}(\text{NH}_2)_2$, and tertiary carbon gives $\text{R}_3\text{C}=\text{NH}$. From the primary carbon we can also derive a triamino compound $\text{R}-\text{C}(\text{NH}_2)_3$, which loses a molecule of ammonia to become $\text{R}-\text{C}(\text{NH}_2)=\text{NH}$. The former is analogous to the ortho acid, while the latter, corresponding with the meta acid, is called an amide-imine or amidine. This formula, unlike $\text{R}-\text{COOH}$ which is stable, can yet lose another molecule of ammonia to furnish $\text{R}-\text{CN}$, a cyanide.

Chloroazodin U.S.P. (Azochoramid) is an amidine derivative with the announced formula $\text{CIN}=\text{C}(\text{NH}_2)-\text{N}=\text{N}-\text{C}(\text{NH}_2)=\text{NCI}$. It is used like the hypochlorites and chloramine-T as a source for nascent chlorine.

Mixed oxygen-nitrogen types of these compounds are also known. As examples we could cite: amides, $\text{R}-\text{C}(\text{NH}_2)=\text{O}$, and their tautomers, $\text{R}-\text{C}(\text{NH})=\text{OH}$; amidoximes, $\text{R}-\text{C}(\text{NH}_2)=\text{NOH}$; hydroxamic acids, $\text{R}-\text{COH}=\text{NOH}$; nitrolic acids, $\text{R}-\text{C}(\text{NO}_2)=\text{NOH}$; hydroxylamines, $\text{R}-\text{NHOH}$ and R_2NOH ; and alkoxy amines, $\text{R}-\text{O}-\text{NH}_2$. There should also be mentioned the derivatives of hydrazine, NH_2-NH_2 , and of semicarbazide, $\text{NH}_2-\text{CO}-\text{NH}-\text{NH}_2$. These, as previously noted, are used in the identification of aldehydes and ketones.

Of these various types the only ones which merit further extensive discussion are the amides and cyanides.

AMIDES

The acylamines constitute a special class of amines because the juxtaposition of the carbonyl group and nitrogen alters the properties. Such acyl compounds can only be derived from primary amines, $\text{R}-\text{CO}-\text{NHR}'$, from secondary amines, $\text{R}-\text{CO}-\text{NR}'_2$, or also from ammonia, $\text{R}-\text{CO}-\text{NH}_2$, but not from tertiary amines. Since these are closely related to the acids, they are generally referred to as acid amides, or simply amides.

The simple ones (from ammonia) are named according to the acid from which they are derived by replacing $-\text{NH}_2$ for $-\text{OH}$. The "ic" and "acid" are dropped to be replaced by "-amide." Thus, acetic acid becomes acetamide in $\text{CH}_3\text{CO}-\text{NH}_2$, while caproic acid becomes caproamide and propionic acid gives propionamide. In the Geneva system "-oic acid" is changed to "-amide" to give such names as methanamide, thanamide, and butanamide.* The other amides are usually designated as alkyl derivatives; $\text{CH}_3\text{CO}-\text{NH}-\text{CH}_3$ might be called methylacetamide, or also acetyl methylamine.

Members of the simple series except formamide are colorless solids with high melting and boiling points, but are often volatile without decomposition. They are easily soluble in water, alcohol, or ether. Diacyl and triacyl derivatives of ammonia are similar in properties.

Preparation.—1. They may be made by the dry distillation of ammonium or substituted ammonium salts of the acids.

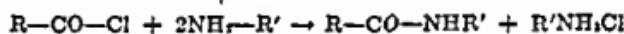


A better yield is obtained if the heat is reduced below the distillation point.

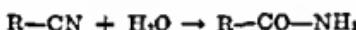
2. Ammonia or its alkyl compounds will act upon esters, anhydrides, or acyl chlorides.



This is the best method for the alkylated amides when the anhydride or chloride is employed.



3. The hydration of cyanides yields the amides as intermediate products, but ordinarily it is difficult to isolate them.



Reactions.—1. Like other amines, they form salts with acids, $\text{R}-\text{CO}-\text{NH}_2\text{--HCl}$, but the basic character of the nitrogen is much weakened by the negative carbonyl, so these salts are very unstable. Indeed, the primary and secondary amides readily undergo tautomerization to $\text{R}-\text{COH}=\text{NH}$ and $\text{R}-\text{COH}=\text{NR}'$, thereby acquiring acid properties; the wandering hydrogen can be replaced by metals to form unstable salts, $\text{R}-\text{CONa}=\text{NH}$ and $\text{R}-\text{CONa}=\text{NR}'$. To indicators the amides are about neutral but to reagents amphoteric.

2. They hydrate to ammonium salts or dehydrate to cyanides with ease, being intermediate in conversion of acids (ammonium salts) to cyanides and vice versa.

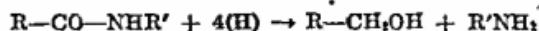


The hydration can be accomplished by boiling with water but more easily with dilute acids or bases, in which case the acid or metal salts are products instead of $\text{R}-\text{CO}-\text{O}-\text{NH}_4$. The dehydration to cyanides will proceed only with the primary compounds and is best performed by heating with phosphorous pentoxide or similar agent. Aldoximes, which are isomeric with the primary amides, will also dehydrate to cyanides.

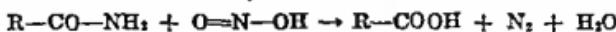


* The system also allows the endings -carbonamide, -carboxamide, and -carboxylamide.

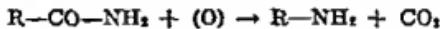
3. Reduction by nascent hydrogen furnishes primary alcohols and ammonia or amines.



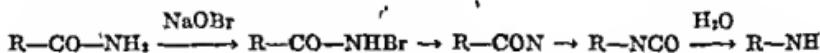
4. Nitrous acid decomposes the simple amides to their acids as might be expected.



5. Alkaline oxidizing agents, notably the hypohromites, react to give primary amines.



This Hofmann degradation probably proceeds in four separate stages, which may be represented as follows:



It is only satisfactory for lower compounds up to about 5 carbon atoms, since otherwise a cyanide is produced. The latter, however, can readily be reduced to a primary amine.

6. Phosphorous pentachloride replaces the carbonyl oxygen by two chlorine atoms. The aminodichloride so produced may lose hydrogen chloride to form a cyanide.

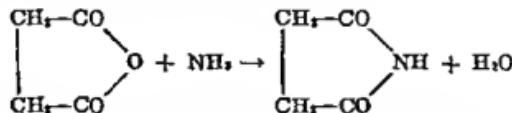


Formamide, $\text{H}-\text{CO}-\text{NH}_2$, is a liquid boiling at 193° . It combines with chloral to yield chloralformamide, $\text{CCl}_3-\text{CHOH}-\text{CO}-\text{NH}_2$, which is sometimes used in medicine as a hypnotic.

Acetamide, $\text{CH}_3-\text{CO}-\text{NH}_2$, crystallizes in needles melting at 82° and boiling at 222° . As encountered in commerce it has a pronounced musty odor, as does also that made in the laboratory, but it is said to be odorless if pure.

Isobutylundecylenamide is the name for a synthetic fly-spray recently reported as superior to pyrethrum.

The action of ammonia on succinic acid anhydride (Chapter XV) gives succinimide.

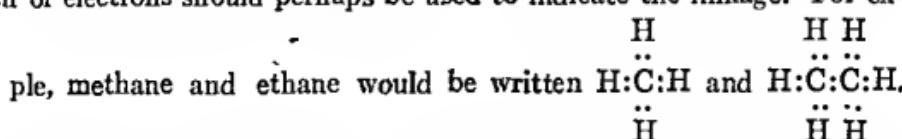


The imino hydrogen by tautomerization is replaceable by metals to yield salts such as Mercuric Succinimide U.S.P.

Electronic Structure.—Before proceeding to the next chapter a few words should be said here about the structure of organic compounds in the light of modern theories. The student has already learned that ionic compounds are presumed to be formed by transference of electrons and that the valence of an element is governed by the number of electrons in its outer shell. Such "polar" valences are the electric forces that unite the ions of electrolytes. In some inorganic compounds, however, a different conception must be used because such transfer is not consistent with atomic structure. Thus, in H_2 the 2 atoms cannot give and receive respectively an electron. We say that there is here non-polar valence and picture the

atoms of hydrogen as sharing their 2 electrons. This is written as H:H using the 2 dots to represent the electrons. This view of covalence is employed generally to explain all non-ionic compounds.

Since practically all organic compounds belong to this class, the shared pair of electrons should perhaps be used to indicate the linkage. For example,



Instead of such formulas, however, we prefer the more economical and efficient system of using a dash or a single dot to represent the linkage. Indeed, we often go still further in rationalized formulas and assume the connection without writing any symbol to show it. There is no advantage in showing all covalent forces and, as long as we know the meaning, no need for doing so.

In the formation of alkylammonium salts and quaternary compounds, we have adopted the older method of increasing the valence of nitrogen from 3 to 5. A consideration of the 5 valence electrons in the outer shell of nitrogen would show us that such a conventional method of increasing valence of nitrogen is misleading. Ammonia must be formed by nitrogen sharing three of its surface electrons with the hydrogen, leaving two of

$$\begin{array}{c} \text{H} \\ | \\ \text{H} : \text{N} : \text{H} \\ | \\ \text{H} \end{array}$$

them unshared, H:N:H. If now ammonia is added to hydrogen chloride, one of these electrons is shared with the hydrogen and the other is transferred in a polar way to the chlorine to make the ionic compound H:N:H Cl.

In the quaternary combinations such as $(\text{CH}_3)_4\text{NCl}$, the electronic formula $\text{CH}_3 +$

$\text{CH}_3 : \text{N} : \text{CH}_3$ takes up only four of the electrons of nitrogen, leaving the CH_3 ,

fifth to be transferred to make the ion Cl^- .

In treating the compounds of nitrogen, it might be advantageous to picture always the electronic formulas. Here again, however, it seems better to leave accepted structure to the imagination in order to economize and simplify. It should be sufficient to write $(\text{CH}_3)_4\text{NCl}$ instead of the known $(\text{CH}_3)_4\text{N}^+ + \text{Cl}^-$, just as in ordinary practice we write NaCl in place of the more accurate $\text{Na}^+ + \text{Cl}^-$.

REVIEW QUESTIONS

1. Write a specific formula for each: a primary, a secondary, and a tertiary amine; salts of each with hydrochloric and sulfuric acids; hydroxide bases of each; some quaternary salt and its base.
2. Name each of the above compounds.
3. What is alkylation? methylation? ethylation?
4. Write equations in steps to show complete methylation of ammonia.

AMINES

5. State four other ways to make amines and illustrate each with equations.
6. Write equations to show formation of salts and of a double salt with platinic chloride, naming each product.
7. Why cannot quaternary bases be liberated from the salts by alkalies? By what means can this be done?
8. Write equations to show the action of nitrous acid on primary, secondary, and tertiary amines and name the products.
9. Write equations to illustrate acylation of primary and secondary amines and the carbylamine reaction.
10. When alkylammonium salts or bases are heated, what are the products? Write an equation to illustrate. Why is this an important reaction?
11. Give formulas for ethylamino, tri-n-propylamino, 2-methylaminobutane, choline, betaine, and mecholyl.
12. How are the ethanolamines made? For what are they used?
13. Represent a lecithin by a specific formula and show how it behaves on hydrolysis.
14. Write the formula of ethylenediamine. In what official compound is it found?
15. How is methenamine prepared? Write equation. By what other names is it known? What is the effect of acids on it? Of what value is this in medicine?
16. For what is chloroazodin used?
17. State three methods for preparing amides and write equations.
18. Name the primary amides of the first five members of the acetic acid series.
19. Show why an amide is amphoteric because of tautomerism.
20. What compounds are formed by hydrating and dehydrating an amide? Illustrate with equations.
21. Write equations to show the action on amides of nitrous acid, hypobromites, nascent hydrogen, and phosphorus pentachloride. What is the Hofmann degradation?
22. Write formulas of formamide, acetamide, butyramide, valeramide, chloralformamide, diacetyl methylamine, succinimide.
23. Write the electronic structure of dimethylamine and of methylammonium chloride.

CHAPTER XVIII

OTHER NITROGEN DERIVATIVES

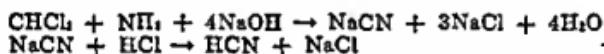
CYANIDES

As has previously been explained, the cyanides may be regarded as triamino substitution products of primary carbon, $R-C(NH_2)_3$, with subsequent loss of two molecules of ammonia to give $R-CN$. They may also be described as alkyl derivatives of hydrogen cyanide, so we should first study this compound.

Hydrocyanic acid or prussic acid, HCN , is a liquid boiling at about 26° and melting at about -15° . It has a characteristic odor somewhat resembling oil of bitter almonds, is miscible with water, burns with a violet flame, and is one of the most rapid of poisons. Diluted Hydrocyanic Acid N.F. contains about 2 per cent of the acid.

It occurs very widely in the vegetable kingdom, sometimes in the free state, but most often combined with other compounds in glycosides. Seeds of many of the *Rosaceae* contain such combinations, notably amygdalin of the bitter almond and other kernels. Wild Cherry U.S.P. furnishes an official syrup that contains some hydrogen cyanide.

The compound may be prepared in many different ways. As examples might be mentioned: the beating of chloroform with ammonia and caustic alkali and liberation by means of a mineral acid



dehydration of formamide with an agent like phosphorus pentoxide, $H-CO-NH_2 \rightarrow HCN + H_2O$; the action of electric sparks on a mixture of acetylene and nitrogen, $CH=CH + N_2 \rightarrow 2HCN$; and the treatment of formaldoxime with boiling water, $CH_2=NOH \rightarrow HCN + H_2O$. The method most often employed is that of treating a metallic cyanide with mineral acid and distilling.



Hydrogen cyanide is so very weak an acid that its alkali salts are decomposed by carbonic acid. It is very unstable even in dilute solution but may be preserved by traces of mineral acids. Warming of such a solution, however, gives hydration to formic acid and ammonia. The multiple union between carbon and nitrogen brings about the possibility of many addition reactions, among which have already been mentioned those with aldehydes and ketones.



Another such addition occurs when it is reduced with nascent hydrogen to an amine.

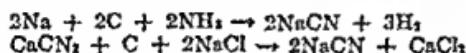


Chlorine reacts with it by chlorination to produce cyanogen chloride, $Cl-CN$.

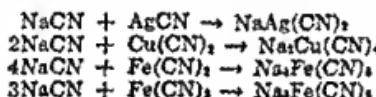
The behavior of hydrogen cyanide, as well as of its metallic salts, appears to show that it consists of a mixture of two isomers, H—C≡N and H—N≡C or H—N=C, which are mutually transformable by wandering of a hydrogen atom. In order to distinguish the formula HNC it is called hydrogen isocyanide.

The metallic cyanides are very important in industry and in analytical chemistry and are probably more or less familiar to the student, but a review of the main aspects of these compounds will not be out of place here.

The alkali salts may be manufactured in several ways but formerly were usually prepared in commerce from waste animal refuse. This was heated with potash and scrap iron to give the double iron cyanide, which upon further heating yielded the alkali salt. Today the best grade is prepared from the action of the metal and carbon upon ammonia at high temperature or by heating calcium cyanamide with carbon and a chloride.



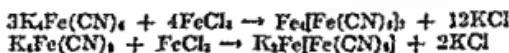
Other metallic cyanides, which are mostly insoluble, can be made by precipitation or by the action of hydrogen cyanide on the oxides or hydroxides. In producing them by the former method, any excess of the reagent tends to dissolve the product to form a soluble double salt.



Sodium cyanide and potassium cyanide, which are described as official reagents, are colorless solids that are as poisonous as the acid. They are sometimes used in medicine as respiratory stimulants. Large quantities are employed in industry for electroplating, for extracting metals from their ores, for production of the acid, and for many other purposes.

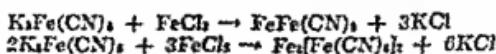
Mercuric Cyanide N.N.R., Hg (CN)₂, is the only common cyanide of heavy metals which is soluble and is also unique among salts in being poorly ionized. Mercuric Oxycyanide N.N.R., Hg(CN)₂.HgO, is used in therapy in the same way.

Potassium ferrocyanide, K₄Fe(CN)₆, also called yellow prussiate, is an official reagent. It gives with ferric salts a precipitate of Prussian blue and with ferrous salts a white precipitate that rapidly turns blue by oxidation.



With cupric ions it gives a brown precipitate of Cu₂Fe(CN)₆, a delicate test for salts of copper.

Potassium ferricyanide or red prussiate, K₃Fe(CN)₆, is also employed officially as a reagent. Its solutions rapidly decompose and should be freshly made just before use. It gives with ferric compounds a brown, soluble salt and with ferrous a precipitate of Turnbull's blue.



Sodium nitroprusside, Na₂Fe(CN)₅NO·2H₂O, another official reagent, is made by the action of nitric acid on sodium ferrocyanide. It gives an

evanescent purple color with dilute solutions of sulfides and is also used to detect acetone and a variety of other substances.

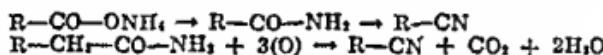
The alkyl cyanides or nitriles are named according to the radical in a manner similar to the halides. Because they hydrolyze to acids, they are called nitriles of these acids, the specific name being formulated by omitting "ic acid" and appending "onitrile." Finally, they may be designated by the Geneva system using "cyano" as analogous to chloro and bromo, or with the suffix nitrile. A few examples will adequately illustrate these three methods.

HCN	hydrogen cyanide	formonitrile	
CH ₃ -CN	methyl cyanide	acetonitrile	cyanomethane
CH ₃ -CH ₂ -CN	ethyl cyanide	propionitrile	ethanenitrile
CH ₃ -CH ₂ -CH ₂ -CN	n-propyl cyanide	n-butyronitrile	cyanoethane
(CH ₃) ₂ CH-CN	isopropyl cyanide	isobutyronitrile	propanenitrile
			1-cyanopropane
			butenenitrile
			2-cyanopropane
			2-methylpropanenitrile

The nitriles are colorless, volatile liquids or solids with pleasant, ethereal odors and are lighter than water. The lower ones are miscible with water but the higher ones are less soluble.

Preparation.—1. The heating of potassium cyanide in alcoholic solution with an alkyl halide is efficient if the latter is primary or secondary. Potassium alkyl sulfates may be substituted for the halide, heated with either alkali cyanide or ferrocyanide.

2. The dry distillation of ammonium salts with dehydrating agents such as phosphorus pentoxide gives the amide as intermediate; hence the amide can be dehydrated in the same way. The Hofmann reaction of hypobromites and amides with more than 5 atoms of carbon gives chiefly cyanide, another method of proceeding from the amides.



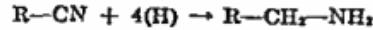
3. Oximes, heated with acetic anhydride or other dehydrating agents, also produce cyanides.



4. The heating of isocyanides sometimes results in rearrangement by wandering of the alkyl group, $R-NC \rightarrow R-CN'$.

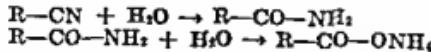
Reactions.—Like hydrogen cyanide the alkyl derivatives are very active, chiefly because of the multiple linkage between carbon and nitrogen.

1. Nascent hydrogen converts them to primary amines by adding at this linkage.



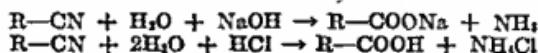
This may be accomplished by sodium and alcohol, by metals with mineral acids, or by hydrogen with catalysts.

2. Water unites with them to form amides and subsequently ammonium salts.

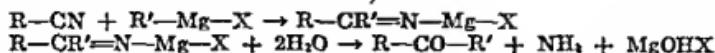


The first step often takes place in the cold, especially in the presence of acids or hydrogen peroxide, and the second step occurs at 100° or above. However, the preparation of lower amides by this process is unsatisfactory.

The rapid conversion to acid can be accomplished readily by boiling with dilute alkali or mineral acid.

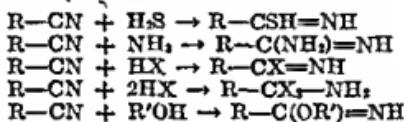


3. The Grignard reagent adds in nitriles to form compounds that hydrolyze to ketones.



It may be recalled that this reaction could be used to make the ketone and that it could be modified to produce aldehyde by employing hydrogen cyanide in place of the nitrile.

4. Many other substances react by addition; the list includes hydrogen sulfide to give thioamides, ammonia to yield amidines, hydrohalogens to amido and imido halides, and alcohols to imido ethers.



Cyanogen, $(\text{CN})_2$, a colorless gas which boils at about -21° , may be prepared by beating the cyanide of mercury or other heavy metals. It behaves chemically like hydrogen cyanide or its alkyl derivatives; for example, it can be hydrolyzed to oxalic acid.

Cyanogen chloride, $\text{Cl}-\text{CN}$, made by the chlorination of hydrogen cyanide, is a very poisonous gas boiling at about 15° . It is a commercial fumigant and has been used in war as a poison gas and lachrymator.

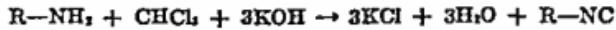
Cyanamide, NH_2-CN , a solid melting at 41° , may be made by the reaction of ammonia on cyanogen chloride or by the dehydration of urea, $\text{NH}_2-\text{CO}-\text{NH}_2$. Its calcium salt, $\text{CaN}-\text{CN}$ or calcium cyanamide, which is employed as a fertilizer, is produced by beating calcium carbide with nitrogen, a process of nitrogen fixation.



ISOCYANIDES

Compounds are also known that correspond with $\text{H}-\text{NC}$ just as nitriles are related to $\text{H}-\text{CN}$. These are called isocyanides, isonitriles, or carblyamines. They are colorless liquids, which boil at a lower temperature than the nitriles, have a characteristic, disagreeable odor, and are very poisonous.

They may be manufactured in the laboratory from primary amines by the so-called carblyamine reaction that involves boiling with chloroform and a caustic base.



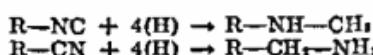
A more convenient method is the heating together of alkyl halide or sulfate with silver cyanide, which also gives some nitrile.



When potassium cyanide is employed the product is largely nitrile, but with some carbylamine. It would be a reasonable conclusion that metallic cyanides are mixtures containing more or less isocyanides.

The carbylamines are even more reactive than their isomers. The structure may be given as $R-N\equiv C$, but the chemical properties suggest $R-N=C=$, since chlorine, oxygen, sulfur, or hydrohalogen will add to the carbon and not to nitrogen also. The compounds formed are respectively: $R-N=CCl_2$ not $R-NCl=CCl$; $R-N=CO$ not $R-NO=CO$; $R-N=CS$ not $R-NS=CS$; and $R-N=CHX$ not $R-NH_2-CX_2$.

All of the isocyanides are easily polymerized and some of them rearrange by heating to nitrile. Reduction leads to secondary amines in contrast to primary amines from the cyanides.

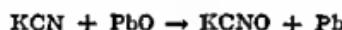


Oxidation gives rise to isocyanates as described in the next section.

ISOCYANATES

These are derived from an unstable cyanic acid, $HCNO$. Assuming that this can exist in two modifications as with $H-CN$, then we should have cyanates from $HO-CN$ and isocyanates from $H-N=CO$. In addition a class of compounds known as fulminates may be regarded as derived from a third isomer, $HO-NC$.

Metal cyanates, which like the cyanides might be mixtures of isomers, are formed by the action of mild oxidizing agents on these cyanides, such as heating with lead oxide or manganese dioxide.



It may be recalled that the transformation of the ammonium salt to urea constituted Wöhler's celebrated experiment in 1828.

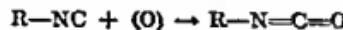


Cyanic acid and its polymer cyanuric acid, $(HO CN)_3$, can be prepared from these metallic salts by metathesis.

When a metallic cyanate is heated with an alkyl halide, there is obtained a volatile liquid with penetrating odor.



This is found to have the structure $R-N=C=O$, since it can also be obtained by oxidizing the carbylamine with mercuric oxide.



In view of the experience with mixtures of isomeric cyanides, we might expect to get here also some of the alkyl cyanate, $R-O-CN$, but these are in fact as yet unknown.

The alkyl isocyanates hydrolyze readily to carbon dioxide and a primary amine, but there is intermediate formation of a urea derivative.



With alcohols they combine to form alkyl carbamic esters, or urethanes, which will be described more fully later.



CHAPTER XIX

SULFUR DERIVATIVES

BIVALENT sulfur may replace oxygen in organic compounds to furnish related substances. The valence of sulfur, however, is frequently 4 or 6, so we might expect many combinations of this element for which there is no oxygen analogue. In general the sulfur derivatives are named by prefixing thio- to the corresponding name of the oxygen compound.

MERCAPTANS

In beginning the discussion of sulfur it will be well to start with simple substitution using the monovalent sulphydryl radical —SH just as we did with —OH for oxygen. If the radical replaces 1 atom of hydrogen in the hydrocarbon, we arrive at R—SH, analogous to the alcohol, R—OH. Compounds containing this sulphydryl group are the thio-alcohols, mercaptans, or thiols.

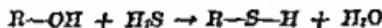
They are generally named as alkyl mercaptans or as sulphydryl hydrocarbons. Thus, $\text{CH}_3\text{—CH}_2\text{—SH}$ is ethyl mercaptan or sulphydrylethane, and $\text{CH}_3\text{—CH}_2\text{—CH}_2\text{—SH}$ is n-propyl mercaptan, or 1-sulphydrylpropane. By a revised Geneva system the prefix mercapto- or the suffix -thiol is directed. The two examples then become ethanethiol or mercaptoethane and propanethiol-1 or 1-mercaptopropane respectively.

The lower mercaptans are colorless, volatile, inflammable liquids, which are insoluble in water but soluble in alcohol or ether. Their boiling points are lower than those of the corresponding alcohols. Those with low molecular weights all have very disagreeable odors; indeed, ethyl mercaptan has a reputation for being the vilest of all substances. The odor is so penetrating that as small an amount as 0.000000005 gram is said to be discernible. Because of this property, mercaptans are sometimes added to fuel gas so that leaks will be detected by odor.

Preparation.—1. The members of this series are prepared from the alkyl halides by warming in alcoholic or aqueous solution with alkali sulfides. Metal alkylsulfates, dialkylsulfates, or alkylsulfuryl chlorides may be used in place of the halides.

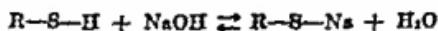


2. They may be manufactured by heating the alcohol or ether with phosphorous pentasulfide or by conducting vapors of the alcohol and hydrogen sulfide over a catalyst (thorium oxide) at high temperature.



3. They are also produced by reduction of other sulfur compounds, such as disulfides, sulfonic acids, sulfenic acids, and thiocyanates.

Reactions.—1. The mercaptans are mild acids and, as such, dissolve to form salts when neutralized by bases.



They are thus more acidic than the alcohols, since the production of alcobolate requires action of strongly basic metals like sodium or calcium. These salts, mercaptides, are very easily hydrolyzed as might be expected and as indicated by the double arrow in the equation given. The names mercaptan and mercaptide were derived from the mercuric salt which was originally called "mercurio corpus aptum" or "mercurium captans."

2. Upon oxidation with nitric acid the sulfur atom is increased in valence and sulfonic acids result.



Conversely, reduction of the sulfonic acid gives a mercaptan. Oxidation with iodine in alkaline solution furnishes disulfides, a reaction which can be used for titration of the mercaptan.



3. Aldehydes and ketones react readily with mercaptans giving compounds analogous to acetals.

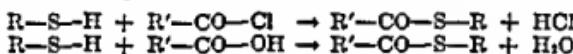


Those from the aldehydes are called mercaptals and those from ketones are called mercaptols or mercaptones.

4. Olefines add the mercaptans under proper conditions to yield sulfides.



5. Acids and their derivatives condense with mercaptans to form thioesters, just as in the preparation of esters from alcohols.



It is notable that water is split out in the latter equation and not hydrogen sulfide, a circumstance that is used as an argument that it is the acid oxygen which forms water in plain esterification.

Methyl mercaptan is said to be the odorous ingredient in the urine after the eating of asparagus and is thought to be produced in intestinal putrefaction. Ethyl mercaptan occurs in several commercial fuel gases. It is claimed that the n-butyl derivative is the odorous matter from the common skunk. "Pentalarm," a pentanethiol, is used in proportions of about one part per million of gas to give warning of escape through its odor.

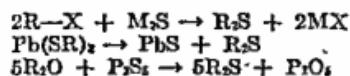
Antimony Thioglycollamide N.N.R., $\text{Sb}(\text{S}-\text{CH}_2-\text{CO}-\text{NH}_2)_3$, and Antimony Sodium Thioglycollate N.N.R., $\text{Sb}(\text{S}-\text{CH}_2-\text{COO})\text{S}-\text{CH}_2-\text{COONa}$, are types of mercaptides that are used in medicine for the content of antimony. The corresponding Thiobismol N.N.R. is a bismuth sodium thioglycollate.

THIO-ETHERS

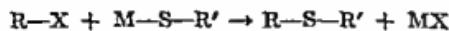
The alkyl sulfides or thio-ethers are $\text{R}-\text{S}-\text{R}'$, being analogous to the ethers and either simple or mixed. They are generally named as dialkyl sulfides, such as diethyl sulfide, but also may be designated as alkylthio derivatives, such as ethylthioethane.

They are very much like the mercaptans in physical properties, including odor which is less intense. Some claim, however, that the sulfides have a pleasant ethereal odor if the compounds are pure.

The simple thio-ethers are prepared by: (1) beating alkyl sulfates or balides with metallic sulfides; (2) dry distillation of mercaptides of divalent metals; (3) heating ethers with phosphorus pentasulfide.



The mixed compounds are best made by (4) beating a mercaptide with the alkyl halide.



Reactions.—The possibility of valence increase by the atom of sulfur brings about ready addition with many reagents.

1. Halogens add to yield crystalline dihalides, R_2SX_2 .
2. Analogous sulfinium or sulfonium salts are produced by addition of alkyl balides.



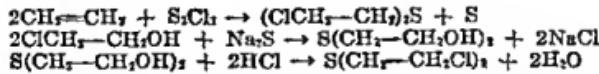
These are soluble, crystalline compounds that again dissociate on heating. By action of moist silver oxide they are converted to oily, caustic sulfinium bases, R_2SOH-R' , entirely analogous to quaternary ammonium bases, R_4NOH , and just as strong.

3. By the action of nitric acid or hydrogen peroxide the sulfides are oxidized to sulfoxides, R_2SO , which are soluble in water and reducible to sulfides again. Further oxidation by concentrated nitric acid yields sulfones, R_2SO_2 , stable solids that cannot easily be reduced again to sulfides.

4. Metallic salts sometimes add to the sulfides to give double salts like $R_2S \cdot HgCl_2$. Such a reaction is used to identify dimethyl sulfide as a contaminator of the official oil of peppermint.

Diallyl sulfide is found in sulfur-containing oils like that of asafetida, as are also dipropyl sulfide and the mixed allylpropyl sulfide.

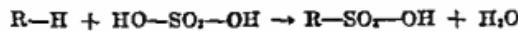
Mustard gas, the blistering agent so often used in warfare, is di- β -chloroethyl sulfide, $(Cl-CH_2-CH_2)_2S$. It is made by the action of sulfur chloride on ethylene or by successive action of sodium sulfide and hydrogen chloride on ethylene chlorohydrin.



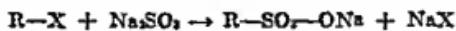
Polysulfides, such as diethyl disulfide ($CH_3-CH_2)_2S_2$, can readily be manufactured in a variety of ways. Diallyl disulfide is said to be the chief odorous material in oil of garlic.

SULFONIC ACIDS

In considering the hydrocarbons it was noted that sulfuric acid could be made to react with them to form sulfonic acids.



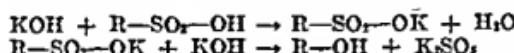
It was also found that mercaptans could be oxidized to these by nitric acid. Similar oxidation of several other varieties of sulfur compounds, such as thio-ethers or thiocyanates, can likewise be used to produce sulfonic acids. A third method of preparation is by heating alkyl halides with sodium or ammonium sulfites, whereby salts result.



When silver sulfite is employed the alkyl esters of sulfurous acid R—O—SO—O—R, are the chief products instead of the sulfonic acids.

The compounds are named by using the prefix sulfo-, or the prefix -sulfonic acid used as a suffix. Thus, $\text{CH}_3\text{—CH}_2\text{—CH}(\text{CH}_3)\text{—SO}_2\text{—OH}$ is 2-butanesulfonic acid or 2-sulfobutane.

The sulfonic acids are colorless oils or very hygroscopic solids, dissolve easily in water, and are not volatile. Since they contain a residue of sulfuric acid, they are very strong acids. Boiling with dilute alkali does not decompose them, but fusion with the base gives a sulfite and the alcohol.



Further reactions of these interesting compounds will be discussed when we take up the derivatives of benzene, where the sulfonic acids are of great importance.

Ichthammol N.F. is a mixture of the ammonium salts of sulfonated bitumens from certain shales. Hirathiol N.N.R., Ichthynat N.N.R., Ichthyol N.N.R., Isarol N.N.R., and Thigenol N.N.R. are very similar, the last instead of shale.

$\text{CH}_3\text{I—SO}_2\text{—ONa}$, or sodium iodomethane-sulfonate, is used in medicine for its content of iodine, 52 per cent.

Taurine, β -aminoethanesulfonic acid or $\text{NH}_2\text{—CH}_2\text{—CH}_2\text{—SO}_2\text{—OH}$, is obtained from the taurocholic acid of bile, which is also a sulfonic acid to be described later.

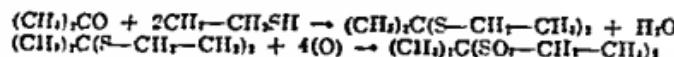
Several sulfonated compounds are marketed as wetting agents; a common one is dioctyl sodium sulfosuccinate (Aerosol O.T.).

DISULFONES

Oxidation of sulfides was found to yield sulfoxides, R—SO—R , and sulfones, R_2SO_2 or $\text{R—SO}_2\text{—R}$. The latter are stable solids that are not conversely reduced to sulfides easily. They can ordinarily be boiled without decomposition.

Mercaptols, noted previously as thio-ethers containing 2 atoms of sulfur, $\text{R}_2\text{C}(\text{SR}')_2$, can be similarly oxidized to disulfones, $\text{R}_2\text{C}(\text{SO}_2\text{—R}')_2$. At least three of these compounds have been used in medicine as hypnotics. All of them can be reduced to mercaptans by heating with carbon.

Sulfonmethane N.F. or Sulfonal is prepared by the reaction of acetone and ethyl mercaptan and subsequent oxidation.



It is a white crystalline powder that is not very soluble in water.

Sulfonethylmethane N.F., originally sold as Trional, is a similar compound but is somewhat more soluble. It is made in the same way using ethylmethyl ketone in place of acetone, hence finally arriving at $\text{CH}_3\text{—CH}_2\text{—C}(\text{CH}_3)(\text{SO}_2\text{—CH}_2\text{—CH}_3)_2$. When diethyl ketone is employed for the starting material, the final product is a tetraethyl compound, $(\text{CH}_3\text{—CH}_2)_2\text{C}(\text{SO}_2\text{—CH}_2\text{—CH}_2)_2$, which has been sold under the title of Tetronal.

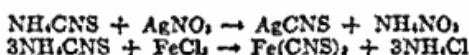
THIOCYANATES

Arbitrary substitution of sulfur for oxygen in cyanic acid gives HCNS or thiocyanic acid. Like the former this compound could be expected to exist in tautomeric forms, H—S—CN and H—N=C=S, and we might also anticipate that it would furnish metal and alkyl derivatives of both classes. Actually this is true of the alkyl compounds, but the metal salts appear to be of the first form and are called thiocyanates. Derivatives of the second would be termed by analogy isothiocyanates.

In the early days different names were given to such compounds and we still find them used at times. The word thiocyanate is in this way considered synonymous with thiocyanide, sulfocyanate, sulfocyanide, rhodanate, and rbodenide. Thus, potassium thiocyanate might even be labelled potassium sulfocyanide, or allyl isothiocyanate might be referred to as allyl isorbadonate.

The metal compounds are prepared from the cyanides or ferrocyanides by beating with sulfur or ammonium polysulfide. They are mostly insoluble, crystalline salts, but those of the alkali metals and a few others are soluble in water.

Potassium Thiocyanate N.F. and Sodium Thiocyanate N.F. are sometimes employed in medicine to reduce vascular pressure. Ammonium thiocyanate, an official reagent, is used to form the white silver salt by precipitation in volumetric analysis or to produce the dark-red ferric salt as a test for ferric ions.

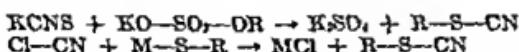


The mercuric compound, $\text{Hg}(\text{CNS})_2$, is often encountered in pyrotechnics as "Pharaoh's Serpents," interesting because of the very luminous ash that is formed from it during burning.

Ammonium Reineckate (Reinecke Salt), $\text{NH}_4[\text{Cr}(\text{NH}_3)_5(\text{SCN})_4] \cdot \text{H}_2\text{O}$, is a pharmacopeial reagent.

Both classes of alkyl derivatives are well-known. They are colorless liquids with characteristic odors and insoluble in water.

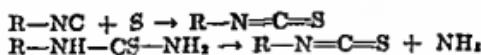
The thiocyanates are produced by distilling a mixture of potassium salt and potassium alkyl sulfate, or of cyanogen chloride and a mercaptide.



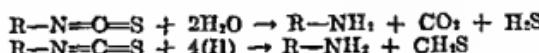
They readily hydrolyze with bases to alcohol and metallic thiocyanate, but in most other reactions the R—S— remains intact. For example, nascent hydrogen reduces them to mercaptan, R—S—H, while fuming nitric acid oxidizes them to sulfonic acids, R—SO₃—OH. The alkyl thiocyanates often rearrange on distillation to the corresponding iso compounds by wandering of the alkyl group from sulfur to nitrogen: R—S—CN → R—N=C=S.

The isothiocyanates are commonly known as mustard oils because the best known of them is the chief ingredient of oil of mustard, formerly official. Several of them are encountered as hydrolytic products from glycosides, especially some in the *Cruciferae* and related families, just as the allyl compound is obtained from sinigrin of mustard.

They can be prepared in the laboratory by heating the normal thiocyanates to boiling as has already been noted, but are usually produced in other ways. The most important methods are the action of sulfur on the carbylamines and deamination of alkylthioureas with syrupy phosphoric acid.



The most important reaction of mustard oils is their addition of ammonia to give alkylthioureas, a reversal of the equation last given. They will also react with water or with nascent hydrogen to yield alkyl amines.



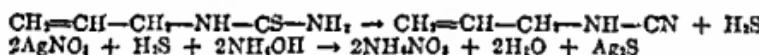
The last compound, obviously thioformaldehyde, is produced as the para polymer (CH_2S)_n.

Allyl Isothiocyanate U.S.P., $\text{CH}_2=\text{CH}-\text{CH}_2-\text{N}=\text{C}=\text{S}$, is the chief ingredient of volatile oil of mustard and is also found in other oils. It is a colorless liquid with a sharp, biting odor and taste, boiling at about 151° and volatile with steam. It is the most efficient of all medicinal blistering agents; local application of the pure substance gives almost instantaneous vesication.

Official assay of allyl isothiocyanate involves addition of ammonia and silver nitrate in alcoholic solution and titration of the excess silver. The first reaction gives thiosinamine or allyl thiourea.



Silver nitrate in the presence of ammonia then withdraws hydrogen sulfide to give allyl cyanamide and a precipitate of silver sulfide.



Other mustard oils which are natural are benzyl, secondary butyl, crotonyl, phenylethyl, and phenylpropyl. They are found in oils of the mustards, cresses, radish, horseradish, and nasturtium.

Other classes of sulfur compounds that are derived by substitution of sulfur for oxygen are naturally quite varied. Every compound that contains oxygen could theoretically have a sulfur analogue and many of them are known. A few illustrations will indicate the variety: thioaldehydes $\text{R}-\text{CHS}$; thioketones R_2CS ; thiolic acids $\text{R}-\text{CO}-\text{SH}$; thionic acids $\text{R}-\text{CS}-\text{OH}$; ditbionic acids $\text{R}-\text{CS}-\text{SH}$.

REVIEW QUESTIONS

1. Write the general formula of a mercaptan, illustrate by three compounds, and name each.
2. How are the mercaptans made from alkyl halides? Write a specific equation to illustrate.
3. Write equations to show formation from thio-alcohols of mercaptides, sulfonic acids.
4. Illustrate by equations the preparation of sulfonium salts, sulfoxides and sulfones.
5. How is mustard gas prepared? Write its formula.

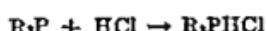
9. State three ways for making sulfonic acids and write equations.
10. What is Ichthammol N.F.? What other medicinal substances are similar in composition and properties?
11. Write the formula of Skiodan N.N.R.
12. How are Sulfonmethane and Sulfonethylmethane manufactured? Write all equations.
13. In what way are the metallic thiocyanates manufactured? Write equations. Which of them are used in medicine?
14. Illustrate by equations the methods by which the alkyl thiocyanates and the mustard oils are prepared.
15. How do the mustard oils behave with ammonia? Write equations for the official assay of allyl isothiocyanate.

CHAPTER XX

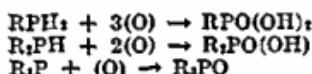
DERIVATIVES OF OTHER ELEMENTS

PHOSPHORUS

As with nitrogen, we consider the phosphorus substitution products as derived from phosphine, PH_3 , and distinguish primary RPH_2 , secondary R_2PH , and tertiary R_3P . While ammonia unites with acids to form ammonium salts, phosphine does so readily only with the hydrohalogens to form phosphonium compounds. Likewise, the alkyl derivatives of phosphine show little tendency to combine with acids or, in other words, have practically no basic properties, although they will unite with hydrohalogens.

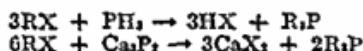


Unlike amines, the alkylphosphines readily take up oxygen, halogens, sulfur, carbon disulfide, and other substances to increase the valence of phosphorus to 5. For example, oxidizing agents act on the three types to give stable phosphonic acids from the primary, phosphinic acids from the secondary, and alkylphosphine oxides from the tertiary.

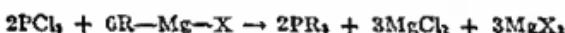


We may regard these as derived from phosphoric acid by substituting alkyl groups for the hydroxyls.

The tertiary compounds are made by action of alkyl halides on phosphine or on metallic phosphides.



They are formed when phosphorus trichloride is treated with metal alkides or with the Grignard reagent.



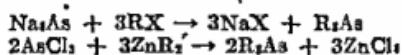
They are inflammable liquids with very unpleasant odor and taste, and are insoluble in water but soluble in alcohol or ether. The secondary and primary compounds are somewhat less stable but possess similar properties. Quaternary salts with the halogens and hydroxides are also known. The latter are very strong bases like the analogous compounds of nitrogen.

ARSENIC

The corresponding combinations of arsenic are much more important because of value in medicine or in the preparation of therapeutic agents. The primary and secondary arsines are distinctly unstable, but furnish stable substances when the residual hydrogen is displaced by chlorine, oxygen, or sulfur. Thus, while CH_3-AsH_2 is very easily decomposed, one can readily prepare CH_3-AsO and $\text{CH}_3-\text{AsCl}_2$. The tertiary arsines are stable, as are also the quaternary salts and bases. Like the analogous phosphines, the valence of arsenic is readily increased by reagents; oxida-

tion gives alkyl arsionic and arsenic acids and arsine oxides, that are similar in character to the corresponding compounds of phosphorus. Arsonic acids, R—AsO(OH)₂, of certain cyclic radicals are important medicinals.

The tertiary compounds are prepared by treating sodium arsenide with alkyl halides or by action of alkides or the Grignard reagent on arsenous chloride.

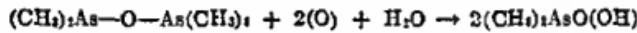


They are sparingly soluble liquids with disagreeable odor and fuming in the air, thereby becoming oxidized to R₂AsO.

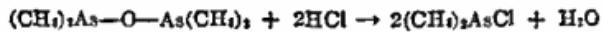
The important secondary arsines are derivatives of cacodyl (from the Greek meaning "stinking") or of its oxide. The latter is produced by distilling sodium acetate with arsenous acid.



The reaction can be used as a test for either arsenic or acetates, because the product has a characteristic, very disagreeable odor. It is usually accompanied by some cacodyl that can be removed by treating with potassium hydroxide or other reagents. The pure oxide is a colorless, insoluble liquid with an unpleasant odor that causes intense irritation, nausea, and stupefaction. It boils undecomposed at about 120° and can be oxidized by mild agents to cacodylic acid.



When the oxide is acted on by hydrochloric acid and mercuric chloride, there is produced cacodyl chloride, which can also be prepared in other ways.



The chloride is a spontaneously inflammable liquid of intense, nauseating odor and boiling at 100°. Chlorine gas converts it to a trichloride, (CH₃)₂AsCl₃, which decomposes on heating to methyl chloride and methyldichloroarsine, a convenient method for producing the primary compound. Oxidation of cacodyl chloride leads to cacodylic acid, just as was the case with the oxide.

Cacodyl itself is best prepared by heating the chloride with zinc in an atmosphere of carbon dioxide.



It is an insoluble, spontaneously inflammable liquid boiling at 170° and possessed of a horrible, nauseating odor. Like other compounds containing trivalent arsenic, it combines easily with chlorine, oxygen, or sulfur.

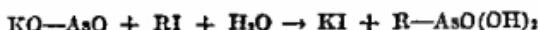
Cacodylic acid, (CH₃)₂AsO(OH), or dimethylarsinic acid, is most conveniently made by heating the oxide with mercuric oxide. It is a soluble, colorless, crystalline substance melting at 200° with decomposition. Sodium Cacodylate U.S.P., (CH₃)₂AsO(ONa)·3H₂O, is a colorless, crystalline salt that is very soluble and deliquescent. Iron cacodylate is also sometimes used.

The useful primary arsines are practically all chlorides. Ethyldichloroarsine, CH₃—CH₂—AsCl₂, was employed as a war gas, as was also the methyl compound. β -Chlorovinyldichloroarsine, used in the same way

under the title of Lewisite, is manufactured by interaction of arsenous chloride and acetylene.



The arsonic acids, $\text{R}-\text{AsO}(\text{OH})_2$, can be made by oxidation of primary arsines or by warming aqueous arsenites with alkyl iodides.



As has been stated, the most important of them are cyclic in character and will be referred to later.

ANTIMONY AND BISMUTH

Primary and secondary derivatives of stibine are unknown, but tertiary compounds are entirely parallel to those of arsenic. Those with low molecular weight are highly disagreeable liquids with an odor like onions and are spontaneously inflammable. Antimony tetralkyl hydroxides, R_4SbOH , and pentalkyls, R_5Sb , have been made. Hundreds of these compounds have been synthesized for use in medicine, most of them cyclic in character.

The comparable compounds of bismuth are very unstable, and those in which bismuth is pentavalent do not exist. This, of course, might be expected because this element, unlike others of the fifth group in the periodic system, is more basic than acidic and usually behaves like the heavy metals such as lead or manganese. For use in medicine in the treatment of syphilis and allied diseases, some more complex combinations of the element have been prepared. These are very much like the tertiary stibines and arsines but are not as disagreeable.

BORON AND SILICON

Trialkyl borides are made by the action of metallic alkides on boron trichloride or ethyl borate. They are liquids of insufferable odor and spontaneously inflammable.

Alkyl derivatives of silicon, SiR_3 , are very stable like the paraffin hydrocarbons, CR_n , that they resemble in stability. The compound of silicon is so closely related to the hydrocarbons that it is an insoluble, mobile liquid similar to its analogue nonane. It would seem possible that one could make compounds in which each atom of carbon in organic substances would be replaced by an atom of silicon. A few examples of such that have already been prepared are: silicochloroform, SiHCl_3 ; triethylsilanol, $(\text{CH}_3-\text{CH}_2)_3\text{SiO}(\text{OH})$; dimethylsilicon oxide, $(\text{CH}_3)_2\text{SiO}$, corresponding to acetone; ethylsilicic acid, $\text{CH}_3-\text{CH}_2-\text{SiO}(\text{OH})_2$, like propionic acid; and ethyl silicon triethoxide, $\text{CH}_3-\text{CH}_2-\text{Si}(\text{OCH}_2-\text{CH}_2)_3$, similar to ortho propionates.

It should also be noted here that silicon can replace carbon completely in organic compounds. Thus, are known a whole series of silicohydrides or silanes, $\text{Si}_n\text{H}_{2n+2}$, that correspond to the methane series. These, of course, are entirely similar to the de that contain oxygen, such as silico-oxy-

Selenium and tellurium can be introduced into organic compounds just as is sulfur, and the resulting products are entirely analogous to the corresponding ones of sulfur.

ORGANOMETALLIC COMPOUNDS

Undoubtedly many of the metallic elements can enter into combination with carbon in hydrocarbons as substituents for hydrogen. Most of the substances of this kind that are already known, however, are of but academic interest, and the combinations of only a relatively few elements warrant discussion in this elementary text. The term organometallic compounds theoretically includes all of those substances in which a metal is linked directly to carbon. It would take in such substances as the acetylides but not salts or alcoholates, in which the metal is linked to oxygen. It is usual, however, to limit the class to derivatives of metals in groups one and two of the periodic table, and we can conveniently limit it still further to group two because other compounds are unimportant, except in one or two instances.

The combinations of metals with hydrocarbon radicals are divided more or less sharply into two classes. In the first are those that are stable to air and water and are generally unreactive. This indifferent character naturally puts them in the category of fairly useless compounds because we can find little of value in organic chemistry for substances that cannot easily be changed. The metals in this group include tin, lead, and mercury. In the second class are compounds that usually decompose in air or with water and are in general quite unstable towards reagents, and the nature of the changes brought about under such conditions make them very useful. The most important elements in this group are aluminum, magnesium, and zinc, and it is with the last two that we are particularly concerned.

The substances that contain magnesium or zinc connected to alkyl radicals are of three types, represented by the formulas MR_2 , $R-M-X$, and $R-M-OH$. Of course, monovalent elements like sodium can form only $M-R$, but trivalent and tetravalent metals like aluminum and lead give a great multiplicity of types. The alkides, MR_2 , are called metal alkyl or alkide and, by the Geneva system, alkyl metal. Examples are $Zn(CH_3)_2$ which is zinc methide, zinc dimethyl, or dimethyl zinc; and $Mg(CH_2-CH_3)_2$ which is magnesium ethide, magnesium diethyl, or diethyl magnesium. The halides, $R-M-X$, are named alkyl metal salts, such as ethyl magnesium iodide, and the hydroxides are designated similarly as alkyl metal hydroxides. Occasionally in complex compounds, especially with mercury, the radicals $-M-X$, $R-M-$, and $-M-OH$ are indicated by prefix, as chloromercuri-, alkylmercuri-, and hydroxymercuri-. Thus, mercurochrome is described as a derivative of 4-hydroxymercurifluorescein.

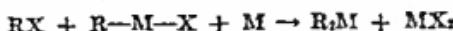
The alkides are generally colorless, mobile liquids or solids and boil without decomposition at low temperature in the absence of air. The alkyl metal halides are solids like salts, and the corresponding hydroxides are solids that ionize more extensively than the related metal hydroxides; thus, $R-Mg-OH$ is a stronger base than $Mg(OH)_2$.

The metal alkyls are usually prepared by one of two methods. In the first the alkyl halide is added to the metal, especially with certain catalytic

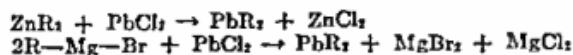
agents, to give as intermediate the alkyl metal halide, which can frequently be isolated.



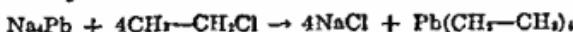
The mixture is then heated in an atmosphere of carbon dioxide or other inert gas.



This method was largely used to make the zinc alkyls so much applied by Frankland in early syntheses. In the second method metal halides are heated with alkides of other metals or with alkyl metal salts. Thus, the compounds of lead, mercury, or tin can be prepared from those of zinc or magnesium.



Lead tetraethyl or "ethyl," which is so extensively used as an anti-knock agent in the automobile engine, is made usually by the reaction of sodium-lead on ethyl chloride.



Zinc Alkyls.—These were discovered in 1849 by Frankland and for many years were employed considerably as valuable aids in synthesis, because of their great activity with various reagents. In recent times, however, they have been largely supplanted by the Grignard compounds. The reactions of the combinations containing zinc appear to be quite comparable in behavior to those containing magnesium, but the ease of handling the latter has relegated zinc more or less to the background.

THE GRIGNARD REAGENT

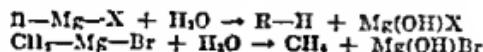
This has frequently been mentioned in earlier pages as a very useful material from which to make many organic compounds. Indeed, representatives of all classes can be prepared synthetically by means of its reactions, and its employment for this purpose has enormously extended the frontiers of organic chemistry.

The general method of use is extremely simple. To a mixture of powdered magnesium and carefully dehydrated ether is added the alkyl halide that has been selected. The bromides and iodides generally react spontaneously, but chlorides need additions such as iodide. If the temperature is allowed to rise, unusual reactions often occur, but this can be prevented by keeping the mixture cool. Other solvents, such as amyl ether or dimethylaniline, can be used in place of ether, but most of them are unsatisfactory.



The product itself can be isolated by evaporation, but in nearly all cases this is unnecessary. The reactant is now added to the ethereal solution and then the mixture is hydrolyzed.

Reactions.—1. Hydrolysis of the reagent without adding any other substance gives hydrocarbons.



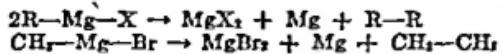
For this decomposition one may add any substance that contains active hydrogen, but it is usually performed by dilute acid or solution of ammo-

nium chloride. Alcohols, ammonia, and amines are among the other substances that might be used. The compound of magnesium that is practically always obtained in any hydrolysis, $\text{HO}-\text{Mg}-\text{X}$, is a basic halide. It may also be written as a mixture of the halide and hydroxide.



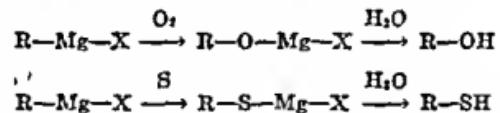
In any event we may refer to it in the future as the Grignard residue and write it $\text{HO}-\text{Mg}-\text{X}$, since its composition is of little importance.

2. If the ether is evaporated and the residue is exposed to heat in an inert atmosphere, a hydrocarbon is also obtained by a combination of two radicals.

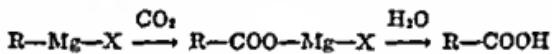


This then becomes essentially the Wurtz reaction (Chapter IV).

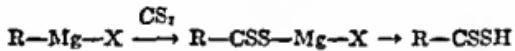
3. Oxygen or sulfur is absorbed by the ether solution, and subsequent hydrolysis furnishes alcohols or mercaptans.



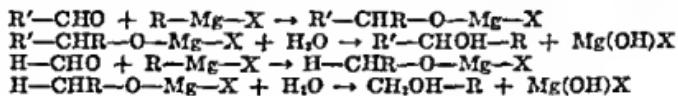
4. If carbon dioxide is bubbled through the cold, ethereal solution, addition takes place readily and subsequent hydrolysis furnishes an acid.



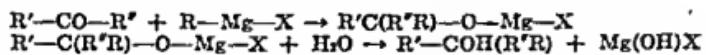
Carbon disulfide, carbonyl sulfide, sulfur dioxide, nitric oxide, nitrogen dioxide, and other similar reagents are added in the same way to give comparable products.



5. Aldehydes add the Grignard reagent at the carbonyl group and the product hydrolyzes to give a secondary alcohol. Formaldehyde, having hydrogen instead of alkyl, gives rise to primary alcohols.



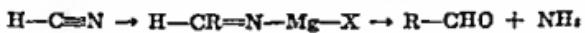
6. Ketones in like manner furnish tertiary alcohols.



7. Cyanides and amides add to the reagent and ultimately produce ketones.

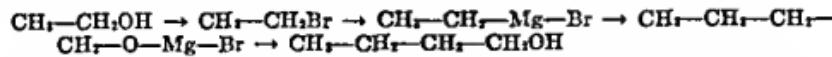


Hydrogen cyanide, on the other hand, gives aldehydes.



8. Ethylene oxide reacts with the reagent to yield $\text{R}-\text{CH}_2-\text{CH}_2-\text{O}-\text{Mg}-\text{X}$ and this hydrolyzes to $\text{R}-\text{CH}_2-\text{CH}_2-\text{OH}$, a primary alcohol. This constitutes a simple and convenient method of adding 2 more carbon atoms to an alcohol, because the alcohol can easily be converted to a

bromide or iodide and this can be used to make the reagent. Thus, ethyl alcohol can be made into butyl alcohol.



Many other reactions of the Grignard reagent are known, but the ones given represent those generally used. With their aid almost any kind of organic substance can be prepared synthetically, and hundreds of the known compounds have been so made. The Grignard reactions represent very valuable processes in the production of new or old compounds. The student is advised to select specific substances of the classes described in previous chapters and devise means for making them through the Grignard process.

It must be admitted in conclusion that, for one reason or another, some halides that should combine with magnesium fail to do so. Still more often we find that certain aldehydes, ketones, and other classes just described resist adding to the reagent. Nevertheless, these instances are few in comparison with the many successful syntheses that have been made in this way.

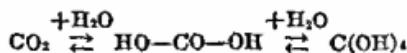
REVIEW QUESTIONS

1. Write formulas of primary, secondary, and tertiary phosphines and for the analogous compounds of arsenic.
2. How does each of the above compounds behave with oxygen and halogens? Write equations.
3. Name each of the oxygen compounds obtained in 2.
4. How are the tertiary phosphines and arsines made? Write equations to illustrate.
5. Write equations to show formation of cacodyl oxide, the chloride, cacodyl, and cacodylic acid.
6. What cacodylate is used in medicine?
7. Write formulas of ethyldichloroarsine and β -chlorovinyldichloroarsine (Lewisita).
8. Why would silicon be expected to replace carbon in organic compounds?
9. How is it made?
10. Write equation.
11. w is it made?
12. .
13. Show by graphic formulas the manner of its addition to carbon dioxide, aldehydes, ketones, oxygen, sulfur, alkyl cyanides, hydrogen cyanide, formaldehyde, and ethylene oxide.
14. Show by equations the hydrolysis of each product in 13.
15. Selecting any one substance that belongs to the classes we have previously discussed, devise a method for producing it by the Grignard process.

CHAPTER XXI

DERIVATIVES OF CARBONIC ACID

IN this chapter we will consider a few substances that are closely related to the familiar carbonic acid, which has existence only in solution. Although it is theoretically like other acids that we have already discussed, yet it is quite unlike them in some respects, and its derivatives are sufficiently important and different to warrant separate treatment. The acid itself is unique in being dibasic without having more than 1 carbon atom. The combining of water with the anhydride, CO_2 , can lead to but two compounds that have only 1 atom of carbon, $\text{HO}-\text{CO}-\text{OH}$ and $\text{C}(\text{OH})_4$.



Although tetraesters of the latter are known and carbon tetrachloride may be looked upon as a derivative, yet it is of little practical importance. The metallic carbonates are all considered as derived from the meta acid, and no salts of the ortho acid are known.

Metacarbonic acid, having two hydroxyl radicals each part of a carboxyl group, will form two sets of derivatives. Thus, we have the monochloride $\text{HO}-\text{COCl}$, the dichloride $\text{Cl}-\text{CO}-\text{Cl}$, the monamide $\text{HO}-\text{CONH}_2$, the diamide $\text{NH}_2-\text{CO}-\text{NH}_2$, the acid ester $\text{HO}-\text{CO}-\text{OR}$, the diester $\text{RO}-\text{CO}-\text{OR}$, and two kinds of salts, normal and acid. In addition many kinds of mixed compounds may be encountered.

Carbonyl chloride, COCl_2 , or phosgene, is a colorless gas boiling at 8° and possessing a suffocating odor. It may be prepared by the direct union of carbon monoxide and chlorine either with the aid of sunlight, as originally discovered in 1812, or using charcoal as a catalyst. Other methods for converting carbon monoxide have been used, but the most convenient one for the laboratory is oxidation of carbon tetrachloride or chloroform by chromic acid or slowly by air.



The ease with which this reaction takes place slowly in the air makes imperative a test for phosgene in chloroform that is designed for anesthesia, because the phosgene is decidedly poisonous; indeed it was first of the gases used during the war of 1914-1918.

Phosgene is very reactive toward a number of substances and, for that reason, is often useful in the preparation of compounds, particularly in the class of dyes. With water it gives a violent action; so strong is this that it can be used for purposes of dehydration, such as conversion of acids to anhydrides.



It acts on alcohols, ammonia, and amines in a similar way to give esters and amides of carbonic acid.

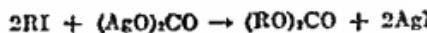


Chloroformic acid, HO—CO—Cl, the monochloride, is not existent, but esters of it are well known. They are formed when the dichloride is added to an excess of an alcohol.

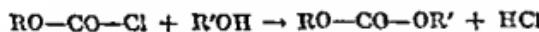


They are used advantageously in synthetic operations for the purpose of introducing carboxyl groups into organic compounds.

The dialkyl esters of carbonic acid may be made in a similar way, as was noted under the reactions of phosgene. They can also be prepared by the heating of alkyl halides with silver carbonate,



or by action of alcohols on esters of chloroformic acid.



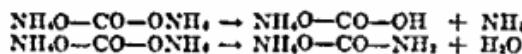
The monalkyl esters are not stable, although they are produced at low temperature by alcohols and carbon dioxide, but inorganic salts of them can be obtained by treating alcoholates with the anhydride.



Potassium ethyl carbonate, a beautifully crystalline solid, is sometimes useful in synthetic operations.

Carbamates.—The monamide of carbonic acid, NH₂—CO—OH, which may be looked upon as aminoformic acid or hydroxyformamide, is known as carbamic acid. Although it has never been isolated, its salts, esters, and other derivatives are important compounds.

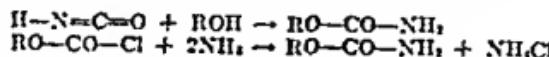
Ammonium Carbonate U.S.P. is described as consisting of varying proportions of ammonium bicarbonate and ammonium carbamate. A study of the formulas shows that the first of these two is formed by loss of ammonia from the carbonate and the second by loss of water.



It should be noted also that the reaction of carbon dioxide, water, and ammonia can lead to any one of the three compounds. Calcium carbamate is soluble in water like the bicarbonate, and its solution is decomposed to the carbonate on boiling.

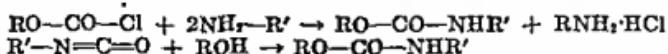


The esters of carbamic acid are of considerable importance in medicine. They are prepared generally by action of an alcohol on isocyanic acid or by treating esters of chloroformic acid with ammonia.

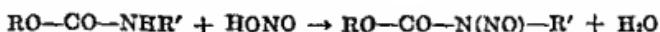


Ethyl Carbamate U.S.P. (Urethane), which is a crystalline solid melting at 45–50° and boiling at 180°, is employed as hypnotic. Similar esters of other alcohols have been used in medicine for the same purpose and are in general known as urethanes. That of methylpropylcarbinol, CH₃—CH₂—CH(CH₃)—O—CONH₂, has been marketed as Hedonal.

Alkyl derivatives of the urethanes, in which the alkyl is substituted for hydrogen of the amino group, are produced by reaction of primary amines on chloroformic esters or of alcohols on alkyl isocyanates.



These compounds, being secondary amines, yield nitrosamines when treated with nitrous acid.

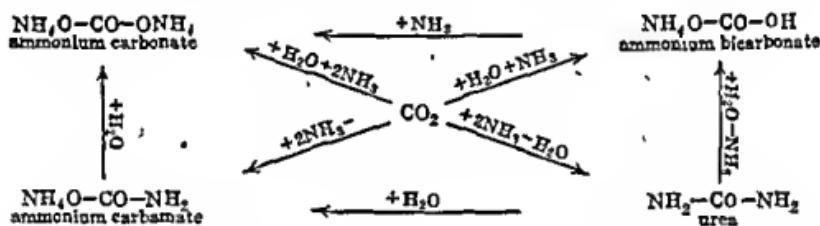


If R' is a methyl group, the compound reacts with strong alkali to give diazomethane.



This yellow gas is a very interesting and valuable substance in synthesis. The alkylurethane, formed from isocyanates and alcohols, is an important means for isolating and identifying the alcohols; the isocyanate usually employed is that of phenyl, C₆H₅, which will be considered later.

Urea.—The diamide of carbonic acid is urea, also known as carbamic amide or carbamide, a crystalline solid melting at 132°, and the chief component of animal urine. Its relation to ammonia, carbon dioxide, carbamates, and carbonates is illustrated by the diagram:



The first synthesis of urea was the classical experiment by Wöhler whereby ammonium cyanate was transformed by internal rearrangement.



Other methods of preparation have since been devised, and today we have available many processes. Among these are the action of ammonia on urethane, ethyl carbonate, or phosgene; the heating of ammonium carbonate in a sealed tube; and the treatment of hot ammoniacal cuprous chloride with carbon monoxide. Technically, hundreds of tons are now made by reaction of carbon dioxide and ammonia under exact conditions of temperature and pressure. This product is employed as a fertilizer and in the preparation of certain kinds of plastics, some also in several other ways. For use in medicine, Urea U.S.P., the commercial article requires some purification.

Because of the two amino groups, urea differs from many other amides in that it forms fairly stable salts with acids. The nitrate, (NH₂)₂CO·HNO₃, is not very soluble and offers a good means for isolating the compound from concentrated urine. The oxalate and other salts can be made in a similar way. It also combines with metal salts in a manner analogous to

water of crystallization; Afenil N.N.R. is such a combination with calcium chloride, $\text{CaCl}_2 \cdot 4(\text{NH}_2)_2\text{CO}$. With mercuric nitrate it combines to give an insoluble substance that can be used for estimation.

The decomposition of urea by sodium hypobromite is employed to estimate the amount in urine.



Secondary reactions occur, so that one must run controls for the amount of nitrogen obtained from pure urea. Conversion of urea to ammonia by means of the enzyme urease can also be used for estimation.



Other reactions of urea are numerous and frequently very useful. Nitrous acid converts it to nitrogen, as is generally the case with primary amines, and carbonic acid.



This furnishes twice as much nitrogen as the hypobromite and can be used similarly for analysis of urine. Chlorine water reacts on urea to give dichlorourea, $\text{CO}(\text{NHCl})_2$. Alcoholic potassium hydroxide and heat transforms urea to cyanates.



Heating with alcohols of a certain type for several hours yields urethanes, a preferable way sometimes to prepare the latter. Biuret, $\text{NH}_2-\text{CO}-\text{NH}-\text{CO}-\text{NH}_2$, is formed by heating urea to 160° , while the corresponding monamide, $\text{NH}_2-\text{CO}-\text{NH}-\text{COOH}$ or allophamic acid, may be made by the action of chlorocarbonic esters on urea. When the nitrate of urea is treated with concentrated sulfuric acid, water is split out to give nitroure, $\text{NH}_2-\text{CO}-\text{NH}-\text{NO}_2$, and reduction of this is a convenient method for making semicarbazide, the compound necessary to form semicarbazones.

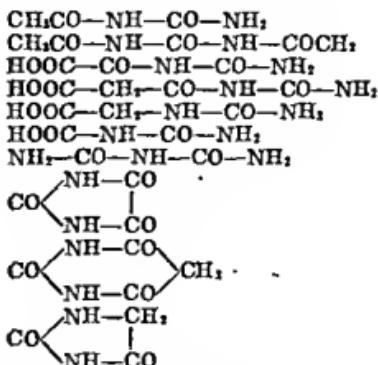


Ureides.—Like all primary amines, urea can be acylated, and the amides so formed are called ureides. There are several types of these because of the two amino groups and because cyclic compounds can be produced with derivatives of polybasic acids. All of them can be hydrolyzed more or less readily, but the cyclic ureides are much more stable than the others. In all of them the basic radicals are connected directly to one or more carbonyls, a condition which it will be recalled reduces the basic character to practically zero. The combination $-\text{NH}-\text{CO}-$ is not only unable to form stable salts with acids, but is in equilibrium with the tautomeric form, $-\text{N}=\text{COH}-$, and the enolic hydrogen is thus acidic to form metallic salts of the type, $-\text{N}=\text{COM}-$. Thus, the ureide $\text{R}-\text{CO}-\text{NH}-\text{CO}-\text{NH}_2$, can be expected to react with $\text{R}'\text{OH}$ to form a stable salt with the formula, $\text{R}-\text{CO}-\text{NH}-\text{CO}-\text{NH}-\text{R}'\text{O}^+$.

Examples of known ureides but only a few can be noted:

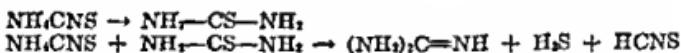
are very important, will be taken up later (Chapter XXXVIII), and one or two examples are given now.

Acetylurea	$\text{CH}_3\text{CO}-\text{NH}-\text{CO}-\text{NH}_2$
Diacetylurea	$\text{CH}_3\text{CO}-\text{NH}-\text{CO}-\text{NH}-\text{COCH}_3$
Oxaluric Acid	$\text{HOOC}-\text{CO}-\text{NH}-\text{CO}-\text{NH}_2$
Malonylurea	$\text{HOOC}-\text{CH}_2-\text{CO}-\text{NH}-\text{CO}-\text{NH}_2$
Glycoluric (Hydantoic) Acid	$\text{HOOC}-\text{CH}_2-\text{NH}-\text{CO}-\text{NH}_2$
Allophanic Acid (Carbonylurea)	$\text{HOOC}-\text{NH}-\text{CO}-\text{NH}_2$
Biuret (Carbamylurea)	$\text{NH}_2-\text{CO}-\text{NH}-\text{CO}-\text{NH}_2$
Parabanic Acid (from oxalic)	$\begin{array}{c} \text{NH}-\text{CO} \\ \\ \text{CO} \end{array}$
Barbituric Acid (from malonic)	$\begin{array}{c} \text{NH}-\text{CO} \\ \\ \text{CO} \end{array}$
Hydantoin (from glycollic)	$\begin{array}{c} \text{CH}_3 \\ \\ \text{CO} \end{array}$



Carbromal N.F. (Adalin) is diethylbromoacetylurea, $(\text{CH}_3-\text{CH}_2)_2\text{CBr}-\text{CO}-\text{NH}-\text{CO}-\text{NH}_2$, and Bromural N.N.R. is 2-bromoisovalerylurea, $(\text{CH}_3)_2\text{CH}-\text{CHBr}-\text{CO}-\text{NH}-\text{CO}-\text{NH}_2$. Both are used as hypnotics but especially like the bromides as sedatives. Barbituric acid is the parent substance of the barbitals which will be considered carefully in Chapter XXXVIII.

Guanidine.—This compound is analogous to urea in that it contains an imide nitrogen in place of the carbonyl, $(\text{NH}_2)_2\text{C}=\text{NH}$. It is, therefore, an amino amidine of carbonic acid. It is a deliquescent, crystalline solid that is soluble in alcohol or water. The compound can be prepared by oxidation of guanine, by heating cyanamide with ammonium iodide, or by heating cyanogen chloride with ammonia. The usual method, however, is to heat thiourea with ammonium thiocyanate at 180° to 190° , although the former is not strictly necessary in the reaction because it is formed from the latter at the temperature used.

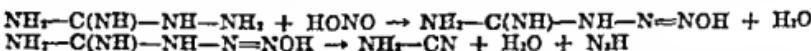


Of course, a salt with the thiocyanic acid is the final product.

Guanidine is a very strong base; it forms stable salts with acids and even absorbs carbon dioxide from the air. Heated alone it forms cyanamide by loss of ammonia, while water hydrolyzes it readily to urea and ammonia. A mixture of nitric and sulfuric acids converts it to nitroguanidine, comparable with nitrourea, and this compound is reducible in the same way to an amine.



The amine can be hydrolyzed to carbon dioxide, ammonia, and hydrazine, NH_2-NH_2 . It can also be converted to diazoguanidine, $\text{NH}_2-\text{C}(\text{NH})-\text{NH}-\text{N}=\text{NOH}$, decomposable by alkalies into hydrazoic acid and cyanamide.



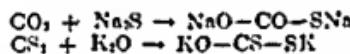
Several derivatives of guanidine, especially alkyl, were tried in medicine as substitutes for insulin but have been abandoned as too toxic. Synthalin and Synthalin-B were the most popular trade names.

Two very important derivatives are creatine and creatinine. The former, $\text{NH}_2-\text{C}(\text{NH})-\text{N}(\text{CH}_3)-\text{CH}_2-\text{COOH}$, is present in animal tissue partly combined with phosphoric acid. A small quantity is excreted daily in the urine in the form of creatinine, its anhydride, $\text{C}(\text{NH})-\text{NH}-\text{CO}-\text{N}(\text{CH}_3)-\text{CH}_2$.

These compounds are really amino acids and will be considered again.

Sulfur Derivatives.—As has been mentioned before, the element sulfur may replace oxygen in practically every organic compound of the latter. Thus, carbon disulfide is the analogue of carbon dioxide, while the mixed carbonyl sulfide, COS, is also known as a colorless gas boiling at -48° . Thiophosgene, CSCl_2 , can be prepared by action of chlorine on carbon disulfide and subsequent treatment with stannous chloride. It is a red, mobile liquid boiling at 73° and more stable to water than phosgene.

The most interesting compounds of this class are the thioearthonic acids and their salts. On theoretical grounds there are five separate acids possible by replacing oxygen of carbonic acid with sulfur: two when this is done once, two if done twice, and one trithio derivative; $\text{HO}-\text{CO}-\text{SH}$, $\text{HO}-\text{CS}-\text{OH}$, $\text{HO}-\text{CS}-\text{SII}$, $\text{HS}-\text{CO}-\text{SH}$, and $\text{HIS}-\text{CS}-\text{SII}$ respectively. The structure of their salts can be inferred from the method of formation, involving CO_2 , COCl_2 , CS_2 , COS, and CSCl_2 , with sulfides or oxides. Thus, the addition of a metallic sulfide to carbon dioxide must yield a monothiocarbonate, while carbon disulfide with an oxide furnishes a dithiocarbonate.



The ethyl acid ester corresponding to the last salt has the formula $\text{CH}_3-\text{CH}_2-\text{O}-\text{CS}-\text{SH}$ and is known as ethyl xanthic acid. Potassium ethyl xanthate is produced by the action of carbon disulfide on alcoholic potassium hydroxide. The copper salt is an unstable, yellow precipitate, to the color of which the name xanthate is derived. Esters with other alcohols are also called xanthic acids. Salts of cellulose xanthates, made by treating cellulose with carbon disulfide and alkalies, constitute the viscose used in the manufacture of rayon.

Analogues of urea and carbamic acid are also known. Salts of dithiocarbamic acid, $\text{NH}_2-\text{CS}-\text{SH}$, and of its alkyl substitution products, $\text{R}-\text{NH}-\text{CS}-\text{SII}$ and $\text{R}_2\text{N}-\text{CS}-\text{SII}$, can be made from ammonia or amines with carbon disulfide. Several of these are of industrial importance. Sodium diethyldithiocarbamate, $(\text{CH}_3-\text{CH}_2)_2\text{NCS}-\text{S}-\text{Na}$, is an official reagent. Thiourea N.N.R., $\text{NH}_2-\text{CS}-\text{NH}_2$, is obtained in methods like those used for urea, most conveniently perhaps by heating ammonium thiocyanate in place of the cyanate in Wohler's experiment. The alkyl derivatives are easily prepared by adding ammonia to mustard oils.



Thiosinamine or allylthiourea, $\text{CH}_2=\text{CH}-\text{CH}_2-\text{NH}-\text{CS}-\text{NH}_2$, from allyl mustard oil, is sometimes used in medicine.

REVIEW QUESTIONS

1. Show by formulas the relation between ortho and meta carbonic acids and carbon dioxide

2. How can phosgene be made from chloroform? Why is this important in chloroform for anesthesia?
3. Why can phosgene be used as a dehydrating agent? Write equation for its action with water.
4. State two methods for making carbonic esters and write equations.
5. Write formulas of ethyl metacarbonate, ethyl orthocarbonate, ethyl chloroformate, and potassium ethyl carbonate.
6. Of what two compounds does ammonium carbonate usually consist? Write equations showing how these are obtained from the last.
7. Write formulas of urethane, carbonyl monamide, and the urethane of methylpropylcarbinol.
8. Show how an alcohol may be identified by means of its reaction with alkylisocyanates.
9. Write equation for the commercial production of carbamide. How was it first synthesized?
10. How can urea be estimated by hypobromite? by urease? by nitrites? Write equations.
11. Write equations for the preparation of semicarbazide from urea.
12. How are ureides made? Write equation for making diacetylurea.
13. Why do ureides form salts with bases? Write an equation to illustrate.
14. Write formulas for carbromal, diethylbromoacetylurea, guanidine, creatine, and creatinine.
15. Write formulas for thiophosgene, a monothiocarbonic acid, potassium ethyl xanthate, ethyl trithiocarbonate.
16. How is thiosinamine made from mustard oil? Write the equation.

CHAPTER XXII

CARBOHYDRATES

T
natural and artificial com-
pou
loscs, dextrins, pentosans,
glycogen, and inulin. They occur in both mnimals and plants, where they
furnish raw, storage, and transport materials in metabolism. Together
with fats and protiens they make up the large bulk of food for man and
animals.

The name for the class was originally selected because most of the
members can be represented by the general formula $C_nH_{2n}O_m$ or $C_n(H_2O)_m$,
making them "carbon hydrates." To apply such a formula as a definition
would mislead, however, since a few compounds of the group differ from
this definition, and also because many other substances that have this
formula are certainly not carbohydrates; as for example acetic acid,
 $C_2H_4O_2$, and lactic acid, $C_3H_6O_3$.

The great majority of carbohydrates can be hydrolyzed to simple mole-
cules called monosaccharides, and all of them either do so or are already
the hydrolytic products. We can define the class, therefore, as *mono-
saccharides or their condensation products*. In recent times this term has
been changed to monoses, as have disaccharides and polysaccharides to
dioses and polyoses. The reason for this renaming may be logical, but the
older system is still preferred by many authorities.

Practically all of the carbohydrates give the so-called Molisch reaction.
The material is mixed with a chloroformic solution of alphanaphthol,
and the whole is superimposed on concentrated sulfuric acid to give a
violet ring between the layers. The color is caused by formation of furfural
through action of the acid.

MONOSACCHARIDES

The monosaccharides or monoses are polyhydric alcohols and also
ketones or aldehydes. In the great majority each carbon is connected to
a hydroxyl group, except that which constitutes the carbonyl. They are
classified and named according to the number of carbon atoms and the
nature of the carbonyl, and are given the ending -ose. An aldohexose is a
polyhydroxyaldehyde with 6 carbons, while a ketopentose is a polyhydroxy-
ketone with 5. Since one must have at least 2 hydroxyls, the minimum
number of carbons is 3. The trioses have the formula $C_3H_6O_3$, the tetroses
 $C_4H_8O_4$, the pentoses $C_5H_{10}O_5$, and the hexoses $C_6H_{12}O_6$. A few natural
monosaccharides are alkyl derivatives, such as rhamnose, $C_6H_{12}O_5$ or
 $CH_3-C_5H_9O_5$, a methylpentose.

Trioses are dihydroxyacetone, $CH_3OH-CO-CH_2OH$, and glyceric alde-
hyde, $CH_3OH-CHOH-CHO$, neither of which is considered in the class
of carbohydrates. The latter may be dextro or levo because of the asym-
metric carbon. The corresponding diose, if allowed, would be glycollic
aldehyde.

Tetroses, $C_4H_8O_4$, also not considered in the class, can exist in two formulas, $CH_2OH-\overset{*}{CHOH}-\overset{*}{CHOH}-CHO$ and $CH_2OH-CO-\overset{*}{CHOH}-CH_2OH$, having 2 and 1 asymmetric carbons respectively. There are, therefore, 4 isomeric aldehydes and 2 isomeric ketones. In such formulas the number of possible compounds can be calculated as 2^n where n is the number of asymmetric carbon atoms, unless meso compounds are possible by symmetry of the molecule. All three pairs of tetroses are known: erythritose, threose, and erythulose.

Pentoses, $C_5H_{10}O_5$.—The aldehydes, $CH_2OH-(CHOH)_2-CHO$, have three asymmetric carbons, making possible four pairs of compounds all of them known. They are d- and l-ribose, d- and l-lyxose, d- and l-arabinose, and d- and l-xylene. Two pairs of ketones should have the formula $CH_2OH-CHOH-CHOH-CO-CH_2OH$ and two pairs the formula $CH_2OH-CHOH-CO-CHOH-CH_2OH$, making a total of 16 possible pentoses, 8 d- and 8 l-. However, in the last formula, which is symmetrical, we have the same condition as in tartaric acid; in one pair the asymmetric carbons oppose each other to give identical compounds, so that there are only 15 pentoses.

As noted we use the symbols d- and l- to designate the opposite pairs. Actually these signs do not refer to the optical rotation but are based upon structural arrangement. They are all compared to the proven configuration of d-glucose (actually dextro), which contains for the primary alcohol

end of the compound $H-\overset{|}{C}-OH$. If the given monosaccharide has the
 CH_2OH

same structure for the comparable end carbon atom, then it is called d- regardless of its optical rotation, and the opposite $HO-\overset{|}{C}-H$ is called l-
 CH_2OH

The formulas for the known aldopentoses are accordingly, using the same representations as for tartaric acid:

$\begin{array}{c} CHO \\ \\ H-C-OH \end{array}$	$\begin{array}{c} CHO \\ \\ HO-C-H \end{array}$	$\begin{array}{c} CHO \\ \\ HO-C-H \end{array}$	$\begin{array}{c} CHO \\ \\ H-C-OH \end{array}$
$\begin{array}{c} \\ H-C-OH \\ \\ CH_2OH \\ d\text{-ribose} \end{array}$	$\begin{array}{c} \\ HO-C-H \\ \\ CH_2OH \\ d\text{-lyxose} \end{array}$	$\begin{array}{c} \\ H-C-OH \\ \\ CH_2OH \\ d\text{-arabinose} \end{array}$	$\begin{array}{c} \\ HO-C-H \\ \\ CH_2OH \\ d\text{-xylose} \end{array}$
$\begin{array}{c} CHO \\ \\ HO-C-H \\ \\ HO-C-H \\ \\ CH_2OH \\ l\text{-ribose} \end{array}$	$\begin{array}{c} CHO \\ \\ H-C-OH \\ \\ HO-C-H \\ \\ CH_2OH \\ l\text{-lyxose} \end{array}$	$\begin{array}{c} CHO \\ \\ H-C-OH \\ \\ HO-C-H \\ \\ CH_2OH \\ l\text{-arabinose} \end{array}$	$\begin{array}{c} CHO \\ \\ HO-C-H \\ \\ H-C-OH \\ \\ CH_2OH \\ l\text{-xylose} \end{array}$

The possible ketopentoses could be represented in a similar way.

None of the pentoses occurs naturally in the free state, but they can be obtained from their condensation products or pentosans by hydrolysis, in the laboratory by degradation or synthetic methods. They are soluble in water, can be reduced by nascent hydrogen to the corresponding pentahydric alcohols, and oxidized to monobasic and dibasic acids. They reduce Fehling's solution and other alkaline solutions of heavy metals. As alcohols pentoses can be acylated to esters or converted to ethers, while as aldehydes or ketones they form oximes and phenylhydrazone. Unlike hexoses, they are not fermentable by yeast or malt. Heated with dilute sulfuric or hydrochloric acid, they are converted to furfural, which can be detected by color reactions or estimated gravimetrically by precipitation with phloroglucinol.

L-Arabinose, melting at 160° and with dextro rotation, is obtained from acacia or from other gums by boiling with acids and is an official reagent. Reduction yields arabinitol and oxidation gives arabinic acid.

d-Xylose* or wood sugar is dextrorotatory. It is produced by hydrolysis of straw, corn-cobs, elder-pith, some gums, and many other substances. It reduces to xylitol and oxidizes to xylonic acid.

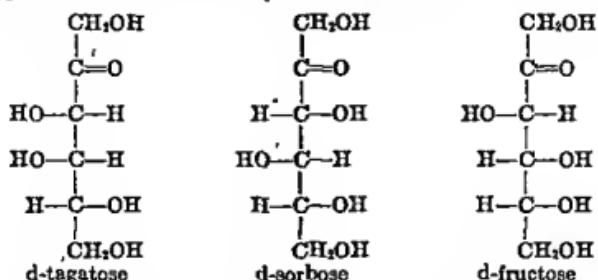
d-Ribose is a constituent of the nucleic acids from nucleoproteins, and is levorotatory. *L*-Rhamnose or isodulcite is a methylpentose that is obtained by hydrolysis of quercitrin, frangulin, and other glycosides. It is an official reagent.

Hexoses.—Exclusive of optical isomers, there can be but one configuration for the aldehydes and two for the ketones, respectively CH₂OH—(CHOH)CHO, CH₂OH—(CHOH)₂CO—CH₂OH, and CH₂OH—CHOH—CO—CHOH—CHOH—CH₂OII. The aldohexoses could exist in eight pairs of isomers because of the four asymmetric carbons, while each of the ketohexose formulas could give 4 pairs, making a total of 16 pairs or 32 hexoses. The 8 *d*-aldohexoses are represented by the formulas given, and the *L*-derivatives would be the mirror images. Fourteen of the 16 are known.

$\begin{array}{c} \text{CHO} \\ \\ \text{H}-\text{C}-\text{OH} \end{array}$	$\begin{array}{c} \text{CHO} \\ \\ \text{HO}-\text{C}-\text{H} \end{array}$	$\begin{array}{c} \text{CHO} \\ \\ \text{HO}-\text{C}-\text{H} \end{array}$	$\begin{array}{c} \text{CHO} \\ \\ \text{HO}-\text{C}-\text{H} \end{array}$
$\begin{array}{c} \\ \text{H}-\text{C}-\text{OH} \\ \\ \text{H}-\text{C}-\text{OH} \end{array}$	$\begin{array}{c} \\ \text{HO}-\text{C}-\text{H} \\ \\ \text{HO}-\text{C}-\text{H} \end{array}$	$\begin{array}{c} \\ \text{HO}-\text{C}-\text{H} \\ \\ \text{H}-\text{C}-\text{OH} \end{array}$	$\begin{array}{c} \\ \text{H}-\text{C}-\text{OH} \\ \\ \text{H}-\text{C}-\text{OH} \end{array}$
$\begin{array}{c} \\ \text{H}-\text{C}-\text{OH} \\ \\ \text{H}-\text{C}-\text{OH} \end{array}$	$\begin{array}{c} \\ \text{HO}-\text{C}-\text{H} \\ \\ \text{H}-\text{C}-\text{OH} \end{array}$	$\begin{array}{c} \\ \text{H}-\text{C}-\text{OH} \\ \\ \text{H}-\text{C}-\text{OH} \end{array}$	$\begin{array}{c} \\ \text{H}-\text{C}-\text{OH} \\ \\ \text{H}-\text{C}-\text{OH} \end{array}$
$\begin{array}{c} \\ \text{CH}_2\text{OH} \\ \\ \text{d-allose} \end{array}$	$\begin{array}{c} \\ \text{CH}_2\text{OH} \\ \\ \text{d-talose} \end{array}$	$\begin{array}{c} \\ \text{CH}_2\text{OH} \\ \\ \text{d-mannose} \end{array}$	$\begin{array}{c} \\ \text{CH}_2\text{OH} \\ \\ \text{d-altrose} \end{array}$
$\begin{array}{c} \text{CHO} \\ \\ \text{HO}-\text{C}-\text{H} \end{array}$	$\begin{array}{c} \text{CHO} \\ \\ \text{H}-\text{C}-\text{OH} \end{array}$	$\begin{array}{c} \text{CHO} \\ \\ \text{H}-\text{C}-\text{OH} \end{array}$	$\begin{array}{c} \text{CHO} \\ \\ \text{H}-\text{C}-\text{OH} \end{array}$
$\begin{array}{c} \\ \text{H}-\text{C}-\text{OH} \\ \\ \text{HO}-\text{C}-\text{H} \end{array}$	$\begin{array}{c} \\ \text{H}-\text{C}-\text{OH} \\ \\ \text{HO}-\text{C}-\text{H} \end{array}$	$\begin{array}{c} \\ \text{HO}-\text{C}-\text{H} \\ \\ \text{H}-\text{C}-\text{OH} \end{array}$	$\begin{array}{c} \\ \text{HO}-\text{C}-\text{H} \\ \\ \text{H}-\text{C}-\text{OH} \end{array}$
$\begin{array}{c} \\ \text{H}-\text{C}-\text{OH} \\ \\ \text{H}-\text{C}-\text{OH} \end{array}$	$\begin{array}{c} \\ \text{HO}-\text{C}-\text{H} \\ \\ \text{H}-\text{C}-\text{OH} \end{array}$	$\begin{array}{c} \\ \text{HO}-\text{C}-\text{H} \\ \\ \text{H}-\text{C}-\text{OH} \end{array}$	$\begin{array}{c} \\ \text{H}-\text{C}-\text{OH} \\ \\ \text{H}-\text{C}-\text{OH} \end{array}$
$\begin{array}{c} \\ \text{CH}_2\text{OH} \\ \\ \text{d-idose} \end{array}$	$\begin{array}{c} \\ \text{CH}_2\text{OH} \\ \\ \text{d-gulose} \end{array}$	$\begin{array}{c} \\ \text{CH}_2\text{OH} \\ \\ \text{d-galactose} \end{array}$	$\begin{array}{c} \\ \text{CH}_2\text{OH} \\ \\ \text{d-glucose} \end{array}$

* The Formulary calls it *L*-xylose, as do also some texts, but most authors say it is *d*-xylose.

At least five of the ketohexoses are also known, the three given and L-sorbose and L-fructose.



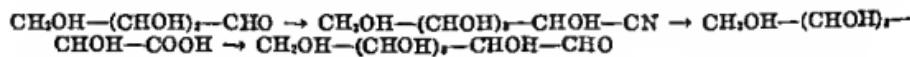
The hexoses are crystalline solids or syrups, soluble in water, less so in alcohol, and almost not at all in ether. They all have a sweet taste, although this may vary in degree. They react with bases like the hydroxides of calcium and strontium to form alcoholates or saccharates, easily decomposed by carbonic acid, and many of them are insoluble.

The alcoholic groups can be acylated and esterified, especially by acetyl chloride, acetic anhydride, or benzoyl chloride, giving up to five acyl groups. They can also be converted to ethers to produce glycosides that will be discussed later.

The hexoses are readily reduced by sodium amalgam to hexatomic alcohols, a property of the carbonyl group.

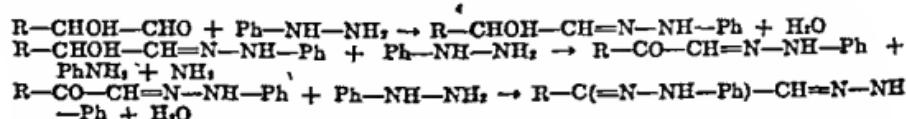
While they are fairly stable in the air at room temperature, other mild and strong oxidizing agents convert them to acids. As reagents for this purpose, solutions of cupric salts are useful to detect and estimate the hexoses as well as some other carbohydrates. Fehling's solution or alkaline copper tartrate, or some modification of it such as Benedict's solution, is very popular, and the alkaline solutions of other heavy metals may be used in a similar way. The products of oxidation will vary with the agent used; from the ketones are obtained acids of lower molecular weight.

The carbonyl group will add in hydrogen cyanide to produce the nitrile of a higher acid. This was used by Fischer to synthesize monosaccharides from one of a lower carbon content, since derivatives of the acid that is formed on hydrolysis can be reduced to aldehydes.



Other addition reactions of the carbonyl group are more difficult and not important; for example, the hexoses do not color Schiff's reagent as do aldehydes generally.

The condensation with primary amines that is typical of the carbonyl group is here very important. Oximes and semicarbazones can be formed, but the reaction with phenylhydrazine is more useful. The crystalline phenylhydrazone so formed can be hydrolyzed to regenerate the hexoses, but they are usually formed with excess of the reagent which oxidizes the neighboring secondary alcohol group and then condenses with the carbonyl so formed.



The resulting crystalline, yellow osazones precipitate out in characteristic forms that are useful for identification of the monosaccharide. Ketoses with the carbonyl in position 2 are converted likewise to osazones, and compounds that are identical except for the first 2 carbon atoms will be changed to the same osazone. For example, d-fructosazone and d-glucosazone are identical. Hydrolysis of these compounds forms ketoaldehydes called osones, $\text{CH}_2\text{OH}-(\text{CHOH})_3\text{CO}-\text{CHO}$. These are easily reduced to ketoses, thus making the series of operations a means for transforming aldoses to ketoses.

Some of the hexoses will ferment with yeast to alcohol, and the ability to do this is apparently bound up with the structure. A multiple of 3 carbon atoms seems essential, but d-glucose will ferment while d-gulose will not.



Dextrose U.S.P. (d-Glucose, Grape Sugar), $\text{C}_6\text{H}_{12}\text{O}_6 \cdot \text{H}_2\text{O}$, occurs very widely distributed in nature, but is usually obtained in commerce by hydrolysis of starch. It constitutes the chief sugar of fruits and is the natural carbohydrate in the blood of animals. In the pure state it is crystalline, melts at 86° , is soluble in water and less in alcohol, and is about five-sixths as sweet as cane sugar. From absolute methanol it is obtained without water, when it melts at 140° . Dextrose can be changed to a phenylhydrazone and to a characteristic osazone melting at 205° . It is reduced by nascent hydrogen to sorbitol and by hydriodic acid to hexyl iodide. Catalytic oxidation is used commercially to make gluconic acid, while treatment with nitric acid gives saccharic acid.

Liquid Glucose U.S.P. is a mixture obtained by the incomplete hydrolysis of starch.

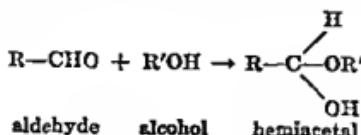
d-Galactose is obtained by the hydrolysis of gums, pectins, and galactans (hemicellulose), and especially from milk sugar along with d-glucose. It is an official reagent.

d-Mannose is found naturally as mannans, being most easily formed by the hydrolysis of the ivory (Brazil) nut. It reduces to mannitol and oxidizes to mannonic acid.

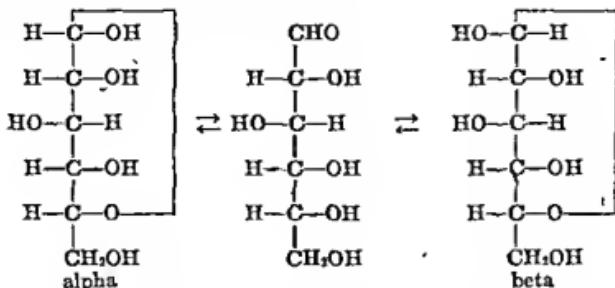
Levulose (fruit sugar, d-fructose) occurs in sweet fruits and honey, and is prepared in the more or less pure state from inulin. Reduction gives sorbitol and mannitol, while oxidation yields glycollic and erythronic acids. It gives a red color with resorcinol and hydrochloric acid (Seliwanoff reaction) distinguishing it from d-glucose and d-galactose. In spite of the name d-fructose it is levorotatory.

d-Sorbose (Sia-sugar, Sianon) is an article of commerce that was originally introduced as a substitute for sugar in the diet of diabetics.

Ring Structure.—The conventional formulas for the monosaccharides as already given are known to be inadequate, although it is much more convenient to use them. There are two isomeric compounds for the names of each hexose; for example, we know alpha and beta forms of d-glucose. These are formulated by tautomerism and production of a ring by a mechanism that is hemiacetal formation within the molecule.

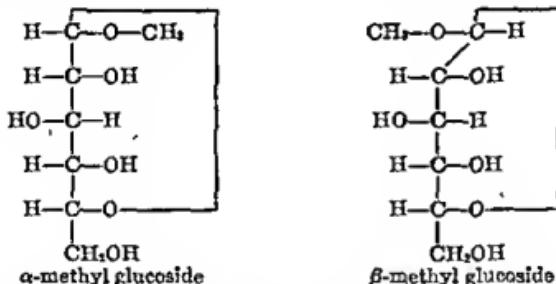


During this tautomerization the aldehyde carbon becomes asymmetric, thus giving rise to the two forms. For D-glucose the alpha form has a rotation of 109° , the beta 20° . When the solid is dissolved in water the rotation is about 100° but gradually changes (mutarotation) to a permanent value of 52.5° , when the various forms are in equilibrium. For other monosaccharides we probably have likewise ring structures and an equilibrium in solution between tautomers.



The ring of 5 carbon atoms and 1 oxygen atom is known as a pyranose ring because of its relation to the heterocyclic compound pyran. In less stable forms of the hexoses, the hemiacetal is produced with carbon atom 4 instead of 5, and the ring so obtained, consisting of 4 carbon atoms and 1 oxygen atom, is designated furanose on account of its relation to furan.

Glucosides are similar to acetals made with other alcohols. Those with methyl alcohol will illustrate.



Like the acetals, these can be readily hydrolyzed to the alcohol and glucose. The natural glucosides are mostly of the beta variety. Other aldoses and ketoses will also furnish such acetals and these are referred to as glucosides, although the general name of glycosides is more in conformity with modern nomenclature.

DISACCHARIDES

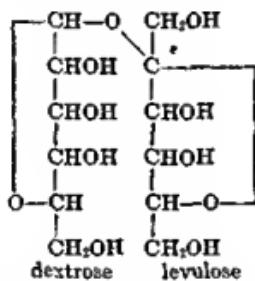
Disaccharides (dioses) are formed by splitting out one molecule of water between two molecules of monosaccharides. The important ones are derived from hexoses and have the empirical formula $C_{12}H_{22}O_{11}$. They are easily crystallizable solids, soluble in water or dilute alcohol, and optically active. They have a sweet taste, and, together with other soluble carbohydrates that have this same property, constitute the class known as sugars. Only some of these disaccharides will reduce alkaline metals and form osazones, and in these a carbonyl group is presumed to be intact in some part of the equilibrium mixture. Fermentation occurs only after

hydrolysis to the monosaccharides. The most characteristic property of the compounds is this ability to hydrolyze under the influence of dilute acids or enzymes. It will be noted that they are for this reason glycosides.

Sucrose U.S.P. (Cane or Beet Sugar, Saccharose), $C_{12}H_{22}O_{11}$, occurs in many plants, especially in the sugar-cane, sugar-beet, maple sap, and the sorghum plant. It is manufactured almost entirely from the first two, giving as by-products molasses, brown sugar, and table syrup. During the process it is purified by conversion to saccharates of calcium or strontium.

Hydrolytic agents transform dextrorotatory ($+65.9^\circ$) sucrose to equimolecular quantities of dextrose ($+52.5^\circ$) and levulose (-98°). Because the sign of rotation is changed, the process is called inversion, and the mixture produced is known as invert sugar. Natural honey approximates this in composition, and an artificial one is made from sucrose by inversion. Honey U.S.P. is used as a flavor and Solution of Invert Sugar N.N.R. is employed like dextrose for sclerosing injections. The hydrolysis of sucrose may be brought about by boiling with dilute acids or by enzymes such as the invertase of yeast. The latter will ferment sucrose to alcohol by the combined action of invertase and zymase. Caramel N.F., used as flavor and color, is made by heating sucrose with a small amount of alkali until the sweet taste has disappeared.

Sucrose is a glucoside of levulose with the probable structure as given. Not being a carbonyl derivative, it does not reduce Fehling's solution or form an osazone.



Lactose U.S.P. (Milk Sugar), $C_{12}H_{22}O_{11} \cdot H_2O$, occurs as the carbohydrate of milk but is very rare in the plant kingdom. β -Lactose is an anhydrous and more soluble form produced by crystallization above 93° . Lactose is quite bland and much less soluble and sweet than sucrose. It will not ferment with yeast but reduces Febling's solution and forms an osazone. Upon hydrolysis it is converted to equimolecular amounts of dextrose and galactose.

Maltose (maltobiose), $C_{12}H_{22}O_{11} \cdot H_2O$, occurs in small amount in all plants that contain starch and comprises a major portion of dry malt. It is usually obtained from starch by the action of diastase; Extract of Malt U.S.P., which contains this enzyme, may be substituted. Maltose is a dextrorotatory (137°) sugar that forms an osazone, reduces Febling's solution, and ferments with yeast by action of maltase and zymase. It hydrolyzes to d-glucose alone when boiled with dilute acids.

Other disaccharides are known but of much less importance. Isomaltose, an intensely sweet sugar from malt, is not readily fermented and furnishes only glucose on hydrolysis. Melibiose, formed from raffinose by yeast, is made up of galactose and glucose, while trehalose or mushroom sugar is

found in moulds, mushrooms, ergot, and manna. Turanose, agavose, and strophantbobioside might also be mentioned.

Trisaccharides are sometimes found in nature. Raffinose or melitriose, $C_{18}H_{32}O_{10} \cdot 5H_2O$, is contained in manna, cottonseed meal, and sugar-beet. It is found in beet sugar to a small extent and in the molasses from its preparation. Although not a reducing sugar, it ferments readily with yeast, which first hydrolyzes it to melihoise and levulose. Emulsin, an enzyme in bitter almond, converts it to sucrose and galactose, and boiling dilute acids give all three of these monosaccharides. Stachyose, from *Stachys tubifera*, and melecitose from larch are other natural trisaccharides.

POLYSACCHARIDES

The condensation of 2 monose molecules liberates 1 molecule of water. The hexoses thus give $C_6H_{12}O_6 + C_6H_{12}O_6 - H_2O$, $C_{12}H_{22}O_{11}$, or $(C_6H_{10}O_5)_2 + H_2O$. Similarly, trisaccharides involve loss of 2 molecules of water and may be represented by $3C_6H_{12}O_6 - 2H_2O$, or $C_{18}H_{32}O_{16}$, or $(C_6H_{10}O_5)_3 + H_2O$. The polysaccharides, containing a large number of monose molecules, may be expressed in like manner. From hexoses the formula would be $n(C_6H_{12}O_6) - (n-1)H_2O$, equivalent to $n(C_6H_{10}O_5) + nH_2O - (n-1)H_2O$, or $n(C_6H_{10}O_5) + H_2O$. With a high value of n the extra molecule of water is almost negligible and usually ignored, giving $(C_6H_{10}O_5)_n$. For those obtained from pentoses in the same way, we would arrive at $(C_5H_8O_4)_n$.

Pentosans.—These saccharides of high molecular weight are found in almost all plants, usually accompanying cellulose in the cell walls. They are insoluble in water and are unaffected by diastase or other amylolytic enzymes, but may be hydrolyzed by boiling with dilute acids to pentoses. They are generally estimated in plant material by conversion of the pentoses to furfural and precipitating with phloroglucinol.

Hexosans. ($C_6H_{10}O_5)_n$, are of immense importance economically, since they include starches, dextrans, celluloses, and glycogen. All of them are insoluble in water, although starch will form a colloidal solution with hot water, and dextrans and glycogen do this in the cold. They do not show any of the reactions characteristic of monoses, but they hydrolyze more or less readily to produce simpler carbohydrates. For each set of 6 carbon atoms there are 3 hydroxyl groups that can be esterified or made into ethers or alcoholates.

Starches.—Starches are found in nearly all plants, but the physical forms are different and probably also the structure. Nevertheless, because all of them give the same products on hydrolysis and in other ways behave alike, they are often referred to indiscriminately as starch. The official article, Starch U.S.P., is obtained from corn, and those from arrowroot and from potato are used as reagents.

Starches are insoluble in water but dissolve in boiling water to a colloidal solution that sets to a paste on cooling or forms an opalescent liquid. This gives a blue color with iodine but does not show any of the reactions characteristic of monoses. If it is boiled with acids, the starch is gradually converted to dextrans, then maltose, and finally dextrose. Diastase, on the other hand, converts it only to maltose. Heat on dry starch, as in the toasting of bread, gives dextrans and other substances.

Dextrin (British Gum), a formulary reagent, is an intermediate product of transforming starch to dextrose by any means. The dextrans are of several types, since some give red or blue colors with iodine and others none at all. They form a colloidal solution with cold water, and the mucilage so formed is employed for making paste, mucilage, and the glue of stamps and labels. The manufacture from starch and separation from other soluble carbohydrates is based on the insolubility of dextrans in dilute alcohol. Commercial dextrin from starch is listed as an official reagent.

Glycogen.—Glycogen or animal starch is the storage form of carbohydrate in the metabolism of animals. The starch of food is converted to dextrose and this is then condensed in the liver and other organs to glycogen. Horse-flesh is particularly rich in this substance and can readily be distinguished from beef by this fact. Glycogen is a white powder that forms an opalescent solution with cold water and gives a red color with iodine. It is very easily hydrolyzed to dextrose by dilute acids or even by water, but is surprisingly resistant to alkalies; sodium hydroxide even up to 60 per cent has practically no effect on it.

Inulin.—Inulin, similar to starch in most properties, occurs in dahlia tubers, the roots of dandelion, chicory, and other plants, and especially in Jerusalem artichokes. It hydrolyzes entirely to levulose and, for that reason, was recommended a few years ago as a substitute for starch in the diet of diabetics. It is an official reagent.

Celluloses, the structural material of plants, are presumably the most complex of hexosans. Cotton, kapok, and filter paper are more or less pure forms, while linen, cotton rags, straw, and wood have other substances in mixture, such as lignin, pentosans, and pectins. Most of the commercial cellulose besides cotton is manufactured from wood. The impurities are largely removed by alkalies or calcium bisulfite, and the fibers are then matted together to make paper or dissolved in reagents to reprecipitate in powdered form.

Cellulose is very slowly hydrolyzed by boiling with dilute acids, but if it is treated with concentrated sulfuric acid and subsequently diluted and boiled, dextrose is the sole product. If the hydrolysis is carried out carefully enough, there is obtained an intermediate disaccharide, a beta glucoside that is called cellobiose. Each one of the dextrose molecules has but 3 hydroxyl groups, but the cellulose molecule is made up of cellobiose units and can, therefore, be converted to a maximum of 6 ester groups. Thus, we may get a cellulose hexanitrate.

If cellulose in the form of paper is treated for a moment with fairly concentrated sulfuric acid and then washed with ammonia, it is changed to a modification known as amyloid. The surface is much smoother and tougher and gives a blue color with iodine. The transformed paper is called parchment.

Mercerized cotton or lisle is a similar modified cellulose made by treatment with a fairly strong solution of sodium hydroxide. The product has a high luster and is dyed more easily than cotton.

The ethers of cellulose are important to the pharmacist in making aqueous or oily solutions more viscous. The different commercial products of methyl cellulose and ethyl cellulose vary in properties with the amount of etherification.

Cellulose nitrates or nitrocelluloses are very useful in a number of ways. The hexanitrate contains theoretically about 14 per cent of nitrogen, while the pentanitrate contains less than 13 per cent, and the others have less. Those compounds with the largest amount of esterification are called high explosives or gun cotton, while those with a lower content are called pyroxylin.

Pyroxylin.—Pyroxylin U.S.P. is manufactured by careful treatment of cotton with a mixture of nitric and sulfuric acids. If the amount of nitrogen in the finished product, which looks like cotton, is much more than 12 per cent, it is less soluble and less usable. Collodion U.S.P. is a solution of pyroxylin in alcohol and ether. If the pyroxylin is modified by treatment with alkali and then dissolved in high boiling solvents, the product is a very useful lacquer, to which other plastic materials are sometimes added. Celluloid is prepared by heating a gelatinized pyroxylin with camphor. The older photographic and movie films are made in a similar manner. Smokeless powder is manufactured from a pyroxylin cotton, gelatinized by various solvents, and nitroglycerin, with the addition of small amounts of other substances. Various kinds of nitrocellulose explosives contain nitrates of other alcohols, as well as nitroglycerin. Finally, nitrocelluloses are employed to make artificial silk; the esters are forced through dies into a saponifying solution, giving more or less pure cellulose in the form of threads.

Acetates.—Acetates of cellulose are also important articles of commerce. They are made by direct esterification with acetic anhydride, and many tons of the latter are used annually for this purpose. The product is soluble in some solvents and can be made to dissolve in others by partial saponification. Applications in industry are transparent wrapping material, safety or slow burning films and plastics, synthetic fibers, and artificial silk.

Cellulose is soluble in Schweitzer's reagent, cupric ammoniobydroxide, and the solution so made is acted upon by dilute acids to reprecipitate the cellulose. This is used in the manufacture of an artificial silk.

Xanthates.—Xanthates of cellulose are prepared by treating the substance with carbon disulfide and alkalies, and the product dissolves in water to form a thick solution known as viscose. From it the cellulose may be regenerated by action of certain reagents, a process that is used to make artificial silk, cellophane, and other materials.

Rayon.—Rayon is a name usually applied to any form of artificial silk but often restricted to a particular variety. With exception of the acetate process, all methods give practically pure cellulose by precipitation from some derivative. The compound or solution is forced through dies of the appropriate shape into a bath containing the regenerating substance in such a manner as to get a continuous thread or sheet. Of the four processes for making rayon, each gives a product that has certain advantages and objectionable features for particular purposes. For example, acetate rayon is not affected by some of the common dyes, and the cuprammonium material is a very excellent one although it is more expensive. The production of the United States in 1936 was distributed in thousand tons as follows: viscose and nitrate 107; acetate 32; cuprammonium 8. The nitrate is estimated as about 12.

Other carbohydrates are of much less importance. Lignin, accompanying cellulose in plants, is not soluble in Schweitzer's reagent and does not give

Thus, the author of the present article believes it is important to point out the following: first, the author of the present article believes that the author of the present article has made a significant contribution to the field of research on the development of the concept of the state in the United States; second, the author of the present article believes that the author of the present article has made a significant contribution to the field of research on the development of the concept of the state in the United States; third, the author of the present article believes that the author of the present article has made a significant contribution to the field of research on the development of the concept of the state in the United States.

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1. The first step in the process of socialization is birth. At birth, the child is born into a family and begins to learn the norms and values of that family. This is the primary source of socialization for the child.

It is not clear if the results of the present study can be generalized to other countries or other ethnic groups.

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the first time in the history of the country.

1. The following table gives the number of hours required for the preparation of the various types of specimens.

1. The following table shows the results of the experiments made by the author on the effect of different concentrations of $\text{Na}_2\text{S}_2\text{O}_3$ on the rate of reduction of Fe^{2+} by H_2 .

For more information about the National Institute of Child Health and Human Development, please go to the NICHD Web site at www.nichd.nih.gov.

1. The first step is to identify the specific needs of the organization.

CHAPTER XXIII

ALICYCLIC COMPOUNDS

THE student is to be reminded at this point that we look upon all organic compounds as hydrocarbons or their substitution products. It should also be recalled that hydrocarbons can be straight chain or cyclic. Having previously discussed the fundamental principles and properties of these chain or aliphatic compounds, we can now turn our attention to those that contain a ring of atoms.

When all of the elements connected in a ring are carbon, the substances are said to be carbocyclic. Since all of the elements are alike, we also use the terms isocyclic or homocyclic, but it is apparent that there might be rings of some other element, and these could also be described by the last two terms. Whenever a ring contains more than one element, the compound is said to be heterocyclic. In our study of the cyclic substances we logically begin with carbocyclic hydrocarbons that are saturated. These and corresponding unsaturated substances, together with their substitution products, are known as alicyclic to indicate the close relation to chain or aliphatic compounds.

CYCLOPARAFFINS

The student will remember that removal of 2 atoms of hydrogen from any one member of the saturated series must lead to a compound containing a double bond or to one characterized by a ring, each with the general formula C_nH_{2n} . Those without the double bond are saturated like members of the methane series, hence are called cycloparaffins. If all of the atoms of carbon are in the ring, each will have 2 atoms of hydrogen and so we have polymethylenes, $(CH_2)_n$. Thus, the two with 3 and 4

atoms of carbon would be CH_2 and CH_2-CH_2 respectively. In technical circles, especially in the petroleum industry, these compounds are also called naphthenes.

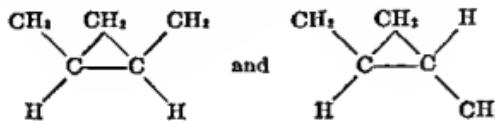
The simple polymethylenes with names, boiling points, and melting points are listed in the table. For comparison the corresponding figures are given for paraffins with the same number of carbons.

		Alicyclic		Paraffin	
Cyclopropane	Trimethylene	m.p.	b.p.	m.p.	b.p.
Cyclobutane	Tetramethylene	-126	-34	-190	-45
Cyclopentane	Pentamethylene	80	+13	135	+1
Cyclohexane	Hexamethylene	90	49	132	38
Cycloheptane	Heptamethylene	+7	81	94	71
Cyclooctane	Octamethylene	-12	119	90	98

Isomerism.—Simple alkyl derivatives of these can have chain isomerism in the entering radical just as with the paraffins, but there can be none according to position of the substituting group because the ring is alike

throughout. Thus, only one methylcyclopropane is possible, although there are two methylpropanes, butane and isobutane. With more than one substitution, however, position in the ring is important, just as it is in the saturated series. The student is urged to write the formulas of dimethyl and trimethyl derivatives of the polymethylenes given in the table; he will find, for example, two dimethylcyclopropanes.

In addition to such differences attributable to position, we may also encounter stereoisomerism in both forms, optical and geometric. The former will depend upon presence of an asymmetric carbon atom, just as it has already been discussed. The geometric form is possible without a double bond because a ring prevents rotation of the carbon atoms in like manner. For example, there should be two compounds that we could designate 1,2-dimethylcyclopropane, represented by the formulas

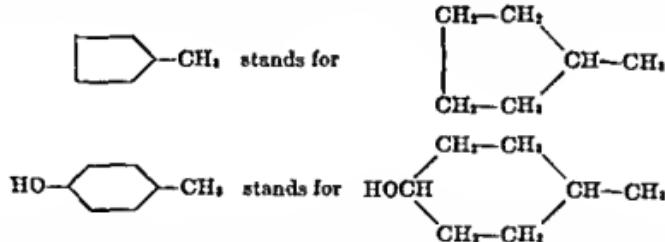


and called respectively *cis* and *trans*. A few minutes with the models will easily convince one of their existence.

In writing the formulas of cyclic compounds it is customary to simplify by leaving out carbon and hydrogen whenever no confusion will result. We then represent the formulas of the first four polymethylenes respectively by the symbols



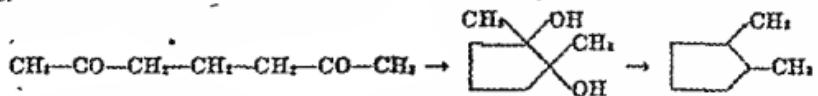
and at each angle understand a carbon and two hydrogens. When substitution has taken place, we simply indicate this by attaching the group in question at the proper point. In order to illustrate two compounds are given, and each is interpreted by a completely rationalized formula.



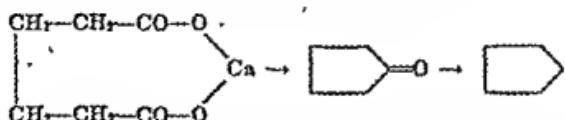
Preparation.—1. The cycloparaffins are made by a reaction that has already been learned. Any dihalide of the formula $X-(CH_2)_n-X$ will be converted to them by withdrawal of the halogen atoms through heating with a metal. Likewise, any dihalide will give a polymethylene or its homologs. Two halogen atoms are not in combination thus, $CH_2-CHBr-CH_2-CH_2Br$ would method is perfectly analogous to the production of a double bond by the same reaction from dihalides that are neighboring, as in $CH_2-CHBr-CHIBr-CH_2$.

2. The reduction of aliphatic diketones leads to cyclic pinacones that can be further reduced by hydriodic acid to the hydrocarbon, a dialkylcyclo-

paraffin. For example, heptanedione-2,6 will yield 1,2-dimethyleyclopentane.



3. Distillation of the salts of dibasic acids furnishes cyclic ketones that can be reduced to the hydrocarbon as usual. Calcium adipate in this way forms cyclopentanone and then cyclopentane.



Many other methods that are familiar to the student are available, but importance of the subject does not warrant more extended discussion. One more should be mentioned, although it cannot be studied fully at present. Reduction of benzene and its derivatives leads to cyclohexane and its substitution products, and this has become an important commercial process.

Reactions.—The cycloparaffins are very similar in most respects to members of the methane series. Chlorine and bromine can halogenate them, but most other reagents are without effect. Like other organic compounds, they can be decomposed by strong oxidation or heat and, under adequate conditions, nitration and sulfonation are effective, but the behavior in these respects is practically indistinguishable from the paraffins.

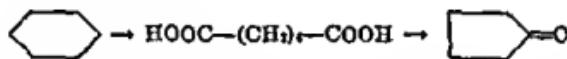
1. In one important way, however, some of them are like the isomeric olefines. Rings containing 3 atoms of carbon, and to a less extent those containing 4, are easily broken by such reagents as hydrogen or hydrogen bromide. Cyclopropane with the latter yields n-propyl bromide, just as propene is changed to isopropyl bromide. Those compounds that contain cycles of 5 or more carbons are very stable under the same conditions. Nascent hydrogen and the proper catalyst will convert cyclopropane to propane at about 80° , whereas cyclobutane requires a temperature of 120° and cyclopentane is not broken under 250° . Rings of more members are not easily so attacked, and this is true with rings up to 34 carbon atoms. It is difficult to prepare such compounds but, once produced, they are very stable.

The explanation of this instability of the lower cycloparaffins is readily apparent by reference to the models, as was first demonstrated by Baeyer in his "strain theory." As was pointed out in Chapter V, the angle between the axes of valence in a tetrahedron is $109^\circ 28'$. In the formation of a double bond between carbon atoms, two of the linkages of either must be redirected to an angle of zero, $C < 109^\circ 28'$ to $C=O$, a change in each of one-half $109^\circ 28'$ or $54^\circ 44'$. This, as we have seen, produces such an abnormal strain that the double bond is easily broken by reagents to relieve that strain. In the formation of a three-member ring, the two connecting bonds of a given carbon atom must be strained from $109^\circ 28'$ to 60° , or $49^\circ 28'$, which means an abnormal direction for each bond of one-half or $24^\circ 44'$. In like manner the amount of strain for each bond

in cyclobutane would be $(109^\circ 28' - 90^\circ) \div 2 = 9^\circ 44'$, and in cyclopentane $(109^\circ 28' - 108^\circ) \div 2 = 0^\circ 44'$. In other words, practically no strain at all should be exhibited when we have a ring of 5 carbon atoms.

With the higher rings one calculates negative abnormalities or strains in the opposite directions, but work with models shows no such actual strains. For cyclohexane we could calculate $-5^\circ 16'$ and for rings of more carbons approaching $-35^\circ 16'$ as a maximum for an infinite number. In a chain of carbons we do not have a straight line, but a zig-zag one in which the angle through any 3 atoms is $109^\circ 28'$. By reference to the models, we can see that only when the number of carbon atoms becomes 5 can we rotate the atoms so that the end ones come near meeting. We can alter those chains of more than 5 carbons so that the ends just meet, no matter how many are in the chain. Hence, we could expect that any ring with more than 4 carbons would be perfectly stable.

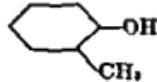
2. Effective oxidation opens the ring to give a dibasic acid, and this may decompose further to compounds of lower molecular weight. It is interesting to note that salts of this dibasic acid decompose on heating to a cyclic ketone with 1 carbon atom less than the cycloparaffin first treated. Thus, cyclohexane is oxidized to adipic acid, and heating the salts of this gives cyclopentanone.



3. If the cycloparaffins or their homologues are heated with selenium, they are oxidized to produce unsaturation. The ultimate product is often a derivative of benzene, and thus this reaction sometimes becomes extremely useful in establishing the constitution of more complicated compounds.

Substitution products of the cycloparaffins are named in the same manner as those of the chain compounds. In numbering, beginning is made at the principal substituent and the lowest number is used. The examples given should make the system sufficiently clear:

2-methylcyclohexanol is



3-hydroxycyclopentanone is



and 1,3-dimethylcyclobutane is



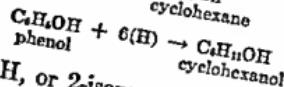
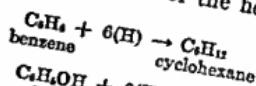
Cyclopropane U.S.P. was introduced into the Pharmacopoeia in 1940 as an inhalation anesthetic.

Cyclohexane, methylcyclohexane, cyclohexanol, and cyclohexanone are now commercial solvents. They are produced by partial or complete

ALICYCLIC COMPOUNDS

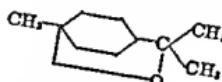
reduction of corresponding compounds of the benzene series that will be described later.

$$\text{C}_6\text{H}_6 + 6(\text{H}) \rightarrow \text{C}_6\text{H}_{12}$$

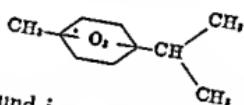


Menthol U.S.P., $C_{10}H_{19}OH$, or 2-isopropyl-5-methylcyclohexanol, is the chief component of peppermint oil. The student will note that carbon atoms 1, 2, and 5 are asymmetric. Accompanying it in the oil are the corresponding ketone, menthone, esters of menthol, and other compounds. Terpin Hydrate U.S.P., $C_{10}H_{20}O_2$, is the hydrate of 1-methyl-4-(1-isopropyl)cyclohexanol. It is prepared by the action of turpentine oil.

Eucalyptol U.S.P. (Cineol), the chief component of eucalyptus oil and found in many other oils, is the inner ether of terpin.

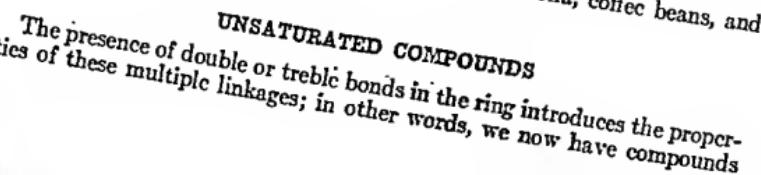



It was formerly assayed by its ability to add acids, a property that is typical of ethers generally (Chapter VII). Ascaridol, which makes up much of Chenopodium oil, is a peroxide that very easily decomposes when heated,



Quercitol or quercite, found in parts of the oak and in other plants is pentahydroxycyclohexane, $C_6H_{12}(OH)_5$. The corresponding hexahydroxy compound, $C_6H_6(OH)_6$, is called inositol, and it is notable in being isomeric with the hexoses. It is found quite widely in plants and animals, not only free but also as methyl ethers, phosphoric esters, and in other ways. The calcium-magnesium salt of inositol hexaphosphoric acid is the phytin used as phosphorus reserve material by green plants. Muscone, $C_{16}H_{30}O$, from the musk deer of Asia, is used in perfumery. It is 3-methylcyclopentadecanone.

Camphor, $C_{10}H_{16}$, is found in camphor oil, which is widely used in perfumery. It is 3-methylcyclopentadecanone, $\text{CH}_3-\text{CH}(\text{CH}_2)_{12}-\text{CO}$. Camphoric acid, $C_{10}H_{12}O_4$, 1,2,2-trimethylcyclopentane-1,3-dicarboxylic acid, is obtained by oxidation of camphor. Mercurin N.R. is the γ -hydroxymercuri- β -methoxypropylamide of camphoric acid, mixed with its sodium salt. Mercurophylline Injection U.S.P. (Mercupurin) is a solution containing mercurin and theophylline. Bismuth Ethylcamphorate N.R. is used like other preparations of bismuth. Quinic acid, $C_6H_7(OH)_2COOH$, is found in cinchona bark and many other plant materials.



like the olefines, polyolefines, or neetylenes. Since we have already become familiar with such structures and their reactivity, it is unnecessary to repeat them here.

The substances are named in the same way as the comparable aliphatic ones, using the suffixes -ene and -yne for double and treble bonds. Thus, 3-methylcyclohexene is $\text{CH}_3-\text{C}_6\text{H}_{10}$.

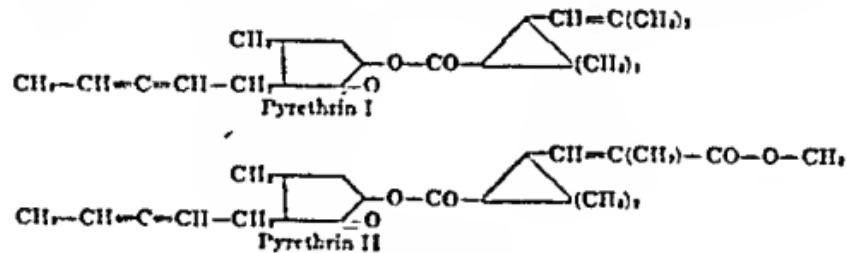
They can be produced in the laboratory by methods that have been learned for the naphthic series. The important processes can be summarized as: treatment of halides with alcoholic alkalies; dehydration of hydroxy derivatives; and removal of halogen from α,β -dihalides by means of metals.

Chaulmoogra acid, the typical acid constituent of Chaulmoogra Oil U.S.P., is a cyclopentenyl derivative of n-tridecyclic acid, $\text{C}_5\text{H}_8-(\text{CH}_2)_{12}-\text{COOH}$. Occurring with it in the official oil is hydrocarpic acid, from hydrocarpus oil, the comparable compound of undecyclic acid, $\text{C}_5\text{H}_8-(\text{CH}_2)_{10}-\text{COOH}$. Ethyl Chaulmoograte U.S.P., a mixture of the ethyl esters of these two acids, is used in medicine like the oil and its acids.

Civetone, a perfumery base obtained from civet, contains a ring of 17 carbon atoms, and has the formula $\text{C}_{17}(\text{CH}_2)_7-\text{CO}$. It is very closely allied to muscone which is used in the same way.

The important compounds in Aspidium U.S.P. are derived from 3,5-dihydroxy-4,4-dimethyl-2,5-cyclohexadienone.

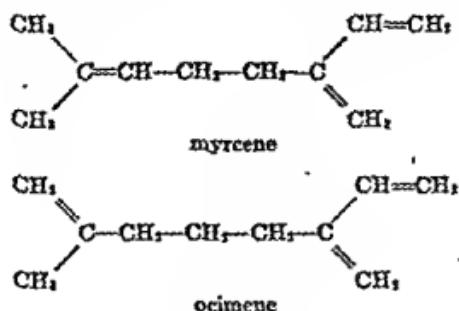
Pyrethrin, the native ingredient of pyrethrum flowers used so much as an insecticide, consists of two derivatives of the cyclopropanins that are more complicated. Their structure has been formulated as follows:



THE TERPENES

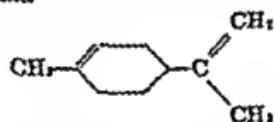
This large class of compounds is widely spread throughout the vegetable kingdom in the volatile oils, and one of them, pinene, is more often found than any other component of the oils. All of the true terpenes have the molecular formula $\text{C}_{10}\text{H}_{16}$ and thus belong to the hydrocarbon group C_nH_{2n} . Since they have 6 hydrogens less than the decanes, $\text{C}_{10}\text{H}_{22}$, they must have a chain with 3 double bonds, a ring and 2 double bonds, 2 rings and a double bond, or 3 rings. For each of these configurations except the last there are several representatives found in nature. These are referred to as aliphatic, monocyclic, and dicyclic respectively.

The aliphatic terpenes are represented by myrcene, named from oil of bay (*Myrcia*), and its isomer ocimene, from oil of basil (*Ocimum*).

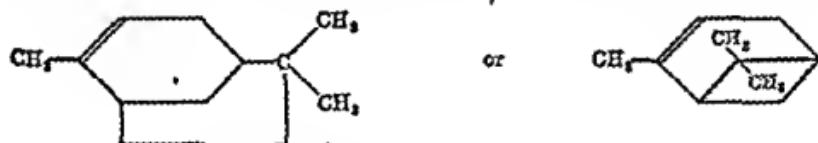


It will be noted that these terpenes are not alicyclic but belong to the class of triolefines.

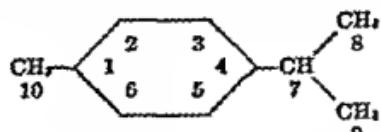
As representatives of the monocyclic terpenes we have: limonene, the chief ingredient of the oils of lemon and orange; the phellandrenes from the genera *Phellandra* and *Eucalyptus*; terpinenes; and several others. The first of these has the formula



Of the dicyclic terpenes we might cite pinene, camphene, and betapinene. Pinene, more often distinguished as alphapinene, is the chief and practically the only constituent of fresh turpentine oil. It has one ring of cyclohexane and one of cyclobutane.



In all of the important cyclic terpenes we find a similar structural pattern, and from this we can get the aliphatic terpenes by opening the ring. This pattern can be referred to 4-isopropyl-1-methylcyclohexane, which is here given the shorter name, terpane.



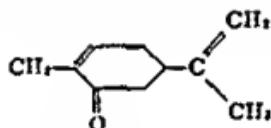
Myrcene is obtained by opening the ring between 3 and 4 and by putting double bonds at 2, 6, and 4,7. Limonene becomes terpadiene—1,7, while pinene is derived by putting a double bond at 1 and completing a second ring by connecting 6 and 7.

All of the cyclic terpenes contain asymmetric carbon atoms and are optically active. Limonene, for example, is found in both dextro and levo forms, and the racemic mixture is of very frequent occurrence under the name of dipentene.

A large share of the components of our commercial oils are substitution products of the terpenes. It would be impossible here to describe each one of the hundreds found, although it might make a fascinating study. All we can do is to point out those that are isolated for use in medicine, or that are notable in some other way. The reactions of each should be recognized by the student because they are just what one would expect from the same functional groups found in the aliphatic series. It might first be mentioned that the aliphatic compounds citral, geraniol, linalol, and citronellol, among other components of volatile oils, have already received notice. The student should recall the formulas of these and note that they conform to the pattern of terpane. Menthol, eucalyptol, ascaridol, and terpin have already been mentioned.

Terpineol, $C_{10}H_{17}OH$, a common ingredient of oils including several of the official ones, is used in perfumery on account of its lilac-like odor. It is 1-hydroxyterpene-7, a tertiary alcohol.

Carvone, $C_{10}H_{16}O$, the chief ingredient of caraway and spearmint oils, is an unsaturated ketone having the formula 6-keto- $\Delta^{1,7}$ -terpadiene or



Pulegone of pennyroyal oil and thujone of arbor vitæ leaves are similar ketones.

POLYTERPENES

If a terpene is decomposed by pyrolysis, one of the main products is isoprene, C_6H_8 , which you will remember is 2-methylbutadiene, $CH_2=C(CH_3)-CH=CH_2$. Polymerization of isoprene proceeds easily, undoubtedly furnishing terpenes as intermediates, but ultimately producing rubber-like resins. Rubber itself upon pyrolysis also gives much isoprene, and attempts to reverse the process have been one of the means used in an effort to get artificial rubber. All of the products may be expressed by the formula $(C_6H_8)_n$; in the terpenes this is 2. It will be observed that the terpenes can be split into two isoprene nuclei, and we will find that many natural compounds can be thus split to these same units.

The sesquiterpenes, $C_{15}H_{20}$, have three isoprene units and one and one-half ($\frac{1}{2}$ -equi) times the molecule of terpene. They are just as widely spread in the oils but are not as well known, because until recently little had been learned of the composition. Having the general formula $C_{15}H_{20-n}$ or 8 hydrogens less than the paraffins, their structures are: 4 double bonds, the aliphatic; 3 double bonds and a ring, the monocyclic sesquiterpenes; 2 double bonds and 2 rings, a dicyclic sesquiterpene; 1 double bond and 3 rings, the tricyclic; and 4 rings, representatives of which are as yet unknown. Cedrolene, a dicyclic compound from juniper tar, is the most common. Zingiberene is a monocyclic sesquiterpene from ginger, while cedarene from cedar is tricyclic. Many more are known.

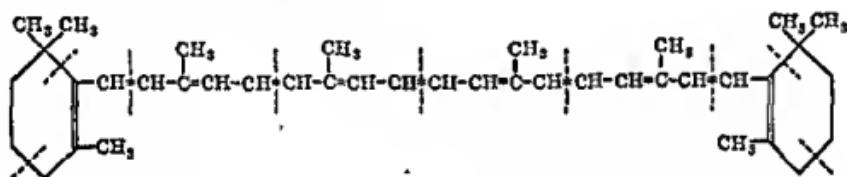
Substitution products from these are also common in the oils. Santalol, the chief ingredient of Sandal Oil U.S.P., is a mixture of two sesquiterpene alcohols, and cedarol of cedar oil is another representative alcohol. Several ketones, aldehydes, and acids of the sesquiterpenes have been isolated.

Diterpenes, and in general polyterpenes, have been recognized in many oils, but in very few has the structure been worked out. There is no doubt, however, that they also consist of several isoprene units.

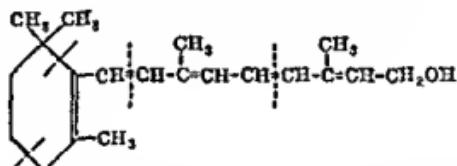
VITAMIN A

Many natural substances are very closely related to the terpenes, other ingredients of the volatile oils, and naturally isoprene. This is particularly true of at least three vitamins, all of the sterols, and all of the sex hormones. Most of these are partly alicyclic, but any detailed discussion would best be postponed, because the rest of the molecule involves new types and reactions; they will be taken up in Chapter XXXIV. We may, however, note here some observations about vitamin A and its provitamins.

It has been known for some time that several natural substances can become converted into A in the body, or at least bring about the same effects in different degree. Among these are the carotenes, part of the coloring matter of carrots, and other carotenoids. The most potent of these is β -carotene, $C_{40}H_{56}$, which consists of eight isoprene units as the dotted lines in the formula show.



In the body it is apparently split in the center and converted to A, $C_{20}H_{30}O$, which has the formula



For this change two molecules of water only are necessary theoretically to convert into two molecules of vitamin A. α -Carotene also gives the effects of the vitamin in the body but in only half the degree; its formula is the same as the beta compound, except that one of the rings has the double bond in a different position, and only one-half of the compound can form the vitamin. The story of the proving of structures and syntheses of these compounds is a fascinating one, but its telling is beyond the scope of this volume.

REVIEW QUESTIONS

1. Define carbocyclic, isocyclic, homocyclic, heterocyclic, cycloparaffin, polymethylene, and alicyclic.
2. Name and write the formulas of the first six cycloparaffins. Which one of these is official?
3. Show how one can have geometric isomerism without a double bond. Illustrate by formulas.
4. State three ways for preparing cycloparaffins and their homologues. Write equations to illustrate.

5. In what respect do the three and four membered rings behave like olefines? How is this explained?
6. Show how effective oxidation changes the alicyclic compounds. What is the effect of heating with selenium?
7. What is a terpene? Name the three classes and give the formula of a member in each class.
8. Write the formulas of menthol, terpin, eucalyptol, ascaridol, and carvone.
9. What is a sesquiterpene? Name two found in oils.
10. Show the relation between terpenes, sesquiterpenes, polyterpenes, rubber, and isoprene.
11. Describe the essential features in the structure of vitamin A and in β -carotene. Why has α -carotene only half the potency of the beta compound?

CHAPTER XXIV

BENZENE AND HOMOLOGUES

IN general the substitution products of benzene and its homologues, together with those closely related substances found in coal tar, are referred to as aromatic compounds. The only existing reason for such designation today is historical because, as we have seen, many of the most odorous of natural materials are alicyclic, a distinctly different class. In the early days of organic chemistry, coal tar proved a prolific source of compounds, many of them of more or less pleasing odor, and most of the then known substances were either aliphatic or aromatic (derivatives of benzene). Even today it can be stated without expectation of argument that many of the important organic substances of commerce are substitution products of benzene. In beginning the study of this class, it will be convenient to start with a brief description of coal tar and its composition.

Coal Tar.—If coal is heated to a high temperature, there is obtained much gas (coal gas), an aqueous solution containing ammonia and a few other soluble compounds, about 6 to 7 per cent of tar, and a residue of coke. The black, viscous, liquid coal tar is refined by distillation to give three or four fractions, leaving up to 60 per cent as a black, solid mass or pitch, that finds industrial application in roofing, insulation, water-proofing, road-making, and other ways. From the distillates by extraction, refractionation, or freezing can be obtained the more or less crude substances that are important. More than 200 compounds have been identified in coal tar, but only a few of these are used industrially. From 100 pounds of coal only about 1 pound of crude substances are utilized, including benzene, toluene, the xylenes, naphthalene, phenols, and anthracene, with much smaller amounts of other compounds. The chief product is naphthalene that amounts to about 0.5 per cent of the coal distilled.

BENZENE

Benzene, C_6H_6 , or benzol, not to be confused with benzin from petroleum which is often pronounced in the same way, is the parent substance of aromatic compounds. It is chiefly obtained from coal tar in which it is found to the extent of 1 to 2 per cent, but it is also present in wood tar, some petroleum, and the destructive distillates of many materials. Indeed, it was first discovered by Faraday in 1825 as a product from whale oil.

Benzene is a mobile, colorless liquid boiling at about 80° and congealing to a colorless solid that melts at 5.5° . It possesses a burning taste and a characteristic odor, burns readily with liberation of much soot, and can accordingly be added to gas for enriching it to produce a luminous flame. It is practically insoluble in water but is miscible with alcohol and other organic solvents, and is itself an excellent solvent for fats, resins, alkaloids, and many other materials. As benzene appears on the market it is frequently adulterated with toluene, carbon disulfide, and especially thiophene. The Pharmacopœia directs a simple test for the latter that will be mentioned later.

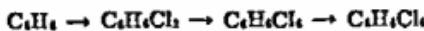
In the laboratory benzene can be prepared from its derivatives by chemical reactions, as by heating phenol (carbolic acid) with zinc or by distilling a mixture of sodium benzoate and soda lime. From aliphatic substances it can often be obtained by pyrolysis, as for example the passing of acetylene through a red-hot tube.



Reactions.—1. Like the paraffins, benzene is readily attacked by chlorine or bromine, but the course of this action depends upon conditions. If cold and in the absence of light, and especially in the presence of a carrier, substitution takes place as with chain compounds.



By further action all 6 hydrogen atoms can be displaced. On the other hand, if the action takes place in strong sunlight, 2, 4, or 6 atoms of halogen are added to the compound exactly as if to polyolefines.



It might again be emphasized that one can tell whether or not halogenation has taken place by testing for hydrohalogen. The addition of halogen to benzene is entirely different from that to olefines because it is much more difficult to accomplish and because bromine water or dilute permanganate have no effect on benzene.

2. While nitration of the paraffins was not practicable in the laboratory, nitric acid attacks benzene very readily to yield nitrobenzene. Indeed, the action must be controlled or it may become quite violent.



For various reasons it is better to add concentrated sulfuric acid as a dehydrating agent. By further action, a second and third hydrogen can be substituted by nitro groups, but one encounters more difficulty in doing so.

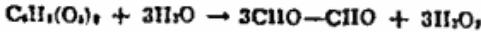
3. Benzene is also acted upon by fuming sulfuric acid at room temperature, or even by the ordinary kind with heat, to produce benzene-sulfonic acid.



4. The molecule of benzene is fairly stable toward reducing agents, but if the action is energetic enough a pair of hydrogen atoms will be taken up, just as is halogen in the light. The introduction of two more pairs is then easy because the first product is the unsaturated cyclohexadiene and the final product is cyclohexane.

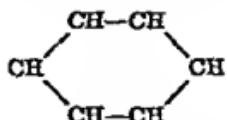


5. Benzene is even more resistant to oxidizing agents, as well as to sodium hydroxide and many other reagents. Ozone, however, will form a triozonide, $\text{C}_6\text{H}_4(\text{O}_3)_2$, that hydrolyzes easily to give glyoxal.



6. Alkyl halides in the presence of anhydrous aluminum chloride will react to split out hydrogen chloride and produce an alkyl benzene (Friedel-Crafts reaction). The temperature must not be allowed to rise too much, and addition of solvents like carbon disulfide often increases the efficiency.

Structure.—In discussing the possible configuration of benzene, it is easy to arrive at a ring of the carbon atoms, each with an atom of hydrogen.

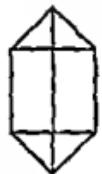


Using the reactions just related, only one mono substitution product can be prepared, showing that all atoms of hydrogen are alike, and the skeleton that is given is the only one consistent with this fact. If one assumed that the carbon has a valence of 3 as given, then this formula would account for most of the chemical properties. However, the facts that hydrogen, halogen, or ozone can be added, even if with difficulty, shows that the fourth valence of each carbon atom must be existent. What to do with it in the formula has been a major problem of the chemist for seventy-five years.

Kekulé, who first visualized ring structure, put in 3 double bonds, but this should have olefinic character and would also necessitate additional position isomerism that is not established.



To overcome this difficulty, Kekulé suggested an oscillating fourth bond. Other formulas that have been suggested are:



Ladenburg



Baeyer



Claus



Dewar

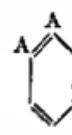
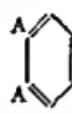
Recent physical experiments have thrown some light on the problem, but it is not yet entirely solved satisfactorily. Some chemists prefer to forget the fourth valence and write the formula , but this can confuse it with cyclohexane. In view of the increasing importance of the latter and its derivatives, it would seem best to favor the original design of alternate single and double bonds for benzene, keeping in mind that this does not indicate a marked capacity to add. We will so use it in the sequel and reserve the plain hexagon for cyclohexane.

Substitution.—We have already noted that, for any one group or radical as substituent for hydrogen, but one compound is known. The formula C_6H_5Cl represents but a single compound, as do also $C_6H_5-NO_2$ and $C_6H_5-SO_2-OH$. The monovalent radical C_6H_5- thus formulated is called phenyl and is frequently abbreviated to $Ph-$, just as ethyl is to $Et-$. It is not an alkyl but in general may again be represented by R , as can other monovalent benzenoid radicals, called collectively aryl (aromatic) and represented by some as Ar in place of R .

With two substituents in place of hydrogen, there should be three isomers, $C_6H_4A_2$.

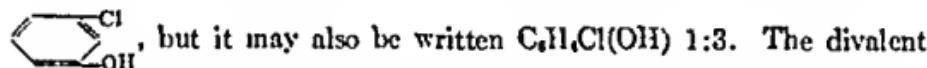


Were one to consider a fixed position of the double bond, it is possible to figure more, but we are obliged to ignore this double bond while still using it to distinguish the benzene ring from that of cyclohexane. We designate the three isomers as ortho, meta, and para respectively. It is important to note that the terms are only relative and that any of the formulas given would not be altered by rotation or reversal. Thus, the ortho refers to two substituents in neighboring position, and the formula that is given might just as well have been any of the following:



The meta position involves one intervening carbon atom, and in the para position the substituents are on opposite sides. In the names of compounds these three terms are abbreviated to o-, m-, and p-; of the formula $C_6H_4(CH_3)_2$, there are three compounds, o-dimethylbenzene, m-dimethylbenzene, and p-dimethylbenzene.

These relative positions are often indicated by numbering. If we started each one of the carbon atoms as 1, we might call o-dichlorobenzene as 1,2 or 2,3 or 3,4 or 4,5 or 5,6 or 6,1 or the reverse of any one of these. In order to get uniformity the rule is to use lowest possible numbers and to put the lower one first, and our compound thus becomes 1,2-dichlorobenzene. The meta compound is 1,3 and the para 1,4. It is customary in writing formulas to use numbers in order to obviate the necessity for using benzene rings. For example, 1-chloro-3-hydroxybenzene has the formula

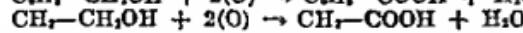
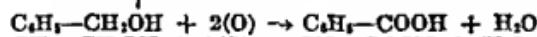
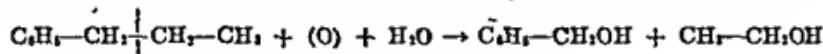


radical $C_6H_4=$ is often called phenylene with specification for position; m-phenylene dichloride is another name for 1,3-dichlorobenzene or $C_6H_4Cl_2$ 1:3.

For three substitutions of like radicals, we find three possible formulas and more if the radicals are dissimilar. The three positions are: 1,2,3 which is called neighboring (*n*) or vicinal (*v*); 1,2,4 which is termed unsymmetrical; 1,3,5 the symmetrical. For four substitutions of like radicals we have also three positions: the neighboring 1,2,3,4; the unsymmetrical 1,2,3,5; and the symmetric 1,2,4,5. Only one compound each is possible for replacement by five or six like radicals. Of course, when the substituting elements or groups are not alike, the number of isomers becomes much higher.

In writing the names of compounds where more than one substituent is present, one of these is often understood as 1 and this number is omitted.

bonds second from the nucleus are broken to introduce hydroxyls (Chapter XI), and the resulting compounds continue to oxidize as usual.



The ultimate effect as far as the ring is concerned, therefore, is the exchange of a carboxyl group for each alkyl side-chain.

5. As in benzene, the nuclear hydrogen is replaceable in the Friedel-Crafts reaction with alkyl halide and anhydrous aluminum chloride.

6. Energetic hydrogenation, or sometimes treatment with hydriodic acid, will add in 6 atoms of hydrogen to form alkylcyclohexanes. The first pair goes in with some difficulty but the remainder much more easily because an unsaturated alicyclic compound is now concerned.

Toluene, $\text{C}_6\text{H}_5-\text{CH}_3$, found in coal tar, is extensively employed in industry for the manufacture of saccharin, T.N.T., chloramines, dyes, benzoates, and many other compounds. It is described as an official reagent. When substitution has taken place once in its nucleus, the resulting radical, $\text{CH}_3-\text{C}_6\text{H}_4-$, is called tolyl, of which there are three, ortho, meta, and para.

The xylenes are also found in coal tar and are used as solvent reagents, usually in the form of a mixture of all three. Oxidation leads to the three isomeric compounds $\text{C}_6\text{H}_4(\text{COOH})_2$. The monovalent aryl radicals, $\text{C}_6\text{H}_5(\text{CH}_3)_2-$, formed by removing a nuclear hydrogen, are known as xylyl.

Mesitylene or sym-trimethylbenzene, $\text{C}_6\text{H}_5(\text{CH}_3)_2$, 1:3:5, is made by the condensation of acetone in the presence of sulfuric acid.

Cymene or p-isopropylmethylbenzene, $\text{CH}_3-\text{C}_6\text{H}_4-\text{CH}(\text{CH}_3)_2$, 1:4, is a by-product of the sulfite process for paper-pulp manufacture. It is closely related to the official thymol and to the terpenes; in fact, it is often found in volatile oils.

Styrene or phenylethylene, $\text{C}_6\text{H}_5-\text{CH}=\text{CH}_2$, is found in coal tar or can be prepared from storax. The unsaturated character makes it useful for polymerization in the manufacture of artificial resins. Phenylacetylene, $\text{C}_6\text{H}_5-\text{C}\equiv\text{CH}$, can be prepared from it by adding bromine and treating the product with alcoholic potassium hydroxide.



Diphenylethylene is known as stilbene and diphenylacetylene is known as tolane: $\text{C}_6\text{H}_5-\text{CH}=\text{CH}-\text{C}_6\text{H}_5$ and $\text{C}_6\text{H}_5-\text{C}\equiv\text{C}-\text{C}_6\text{H}_5$.

Diphenyl or phenylbenzene, $\text{C}_6\text{H}_5-\text{C}_6\text{H}_5$, is another of the compounds found in coal tar, but it is usually prepared by heating benzene or benzoic acid to red heat or passing the vapors over molten lead.



In the laboratory it is made by heating benzene on a charcoal solution of iodobenzene. It is a colorless liquid, b.p. 270°–271° at 760 mm., at 254°. On account of its great stability it is a powerful bleaching agent.

latent heat, it is used in commerce under the name Xenene as a heat transfer agent, also for other purposes.

Diphenylmethane, $C_6H_5-CH_2-C_6H_5$, is a solid with a geranium-like odor and is used in soaps and the manufacture of dyes.

Triphenylmethane, $(C_6H_5)_3CH$, forms the basis of an important class of dyes (Chapter XLI). It is a weak acid, forming a sodium salt, $(C_6H_5)_3CNa$, when treated with sodium in liquid ammonia. The methane hydrogen is easily oxidized to a hydroxyl group. Tetraphenylmethane is also known.

The radical triphenylmethyl, $(C_6H_5)_3C-$ was isolated by Gomberg in 1900 when he treated the chloride with silver. It was found to be extremely reactive toward many reagents. This is an excellent illustration of the rarely accomplished liberation of free radicals.

Orientation Rule.—When there is one substitution in benzene and we desire to introduce another, it is sometimes advantageous to know where this will go. Although there is never quantitative entrance at one given position, and nearly always some of each of the three possible compounds is formed, yet for the main product there is a definite rule, first formulated by Crum Brown. The position mainly attacked depends entirely upon the character of the substituent that is already present; if it is of one class the new group will enter in meta position, but if of the other class in para and ortho simultaneously, usually the largest amount in the former. The meta-directing groups include $-NO_2$, $-COOH$, $-SO_2OH$, $-CHO$, $-CO-R$, and $-CN$, and it is noteworthy that in each the atom connected to the nucleus is linked to some other element by a double bond. The para-ortho-directing groups are $-X$, $-R$, $-NH_2$, $-NHR$, $-NR_2$, $-OH$, etc.; in these cases the connected atom has no double bond.

Two illustrations for the operation of this rule will make it clear. If nitrobenzene is chlorinated, the chief product will be m-chloronitrobenzene, but if chlorobenzene is nitrated the nitro group will go largely in ortho and para position. In the first reaction some ortho and para are also produced and in the second we will obtain a small amount of meta. Again, should toluene be nitrated or sulfonated the main yield would be para and ortho, but if benzoic acid, C_6H_5-COOH , were submitted to either of these processes, mostly meta compounds would be obtained.

Another interesting generalization is found in the ease with which second substitutions take place. If an ortho-para-directing group is already present, the second substitution is easier. Consequently, the introduction of a third substituent is more difficult to carry out than in benzene itself.

The question of where a third group will enter the ring can also be answered in many cases. It is unnecessary to discuss the matter thoroughly, but we might consider some cases, using CH_3 and NO_2 as illustrations of para- and meta-directing radicals. If two nitro groups are meta to each other, both point to position 5. If CH_3 and NO_2 are 1:2, the new group will enter 4 or 6 because both orient that way. If two methyl radicals are meta to each other, the position indicated would be 2. In all of these one substituent reinforces the other. In those cases where they are working contrariwise, we could expect to get rather a heterogeneous mixture of products. The different radicals vary in degree of influence, however, and one can often predict what will be the chief result.

REVIEW QUESTIONS

1. What is meant by an aromatic compound? an aryl group?
2. What are the chief substances found in coal tar?
3. What is the chief source of benzene? How is it usually produced in the laboratory?
Write the equation.
4. Under what conditions will halogenation of benzene take place? When will addition of halogen occur? Write equations for the reactions.
5. Write equations to show nitration, sulfonation, reduction, and the Friedel-Crafts reaction.
6. Write the formulas of phenyl chloride, o-dihromobenzene, metachlorotoluene, p-nitrobenzenesulfonic acid, m-phenyfene dichloride.
7. Name $C_6H_5(CH_3)_2$ 1:3 and $C_6H_5(NO_2)_2$ 1:3:5.
8. State five ways for making the homologues of benzene and give an equation illustrating each.
9. Under what conditions does halogenation take place in the nucleus and in the side-chain? Write equation for each reaction.
10. Write equations to show oxidation of isopropylbenzene and of diethylbenzene.
11. Give the structural formulas of toluene, the three xylenes, cymene, styrene, diphenyl, triphenylmethane.
12. Write equations for the nitration of toluene, the sulfonation of C_6H_5-COOH , and the chlorination of nitrobenzene.
13. Write the formulas of all isomers corresponding to C_6H_5ClBr , $C_6H_5Br_2$, and $C_6H_5(OH)_2$ and name each.
14. Outline a method for synthesizing toluene from the elements.

CHAPTER XXV

DIRECT SUBSTITUTION PRODUCTS

HALIDES

THOSE compounds formed by introduction of halogen for hydrogen in the nucleus of benzene and its homologues are named as has already been described. They are generally insoluble, colorless liquids or solids and are less inflammable than the hydrocarbons, but they are quite volatile, especially with steam, and give irritating, lacrymatory vapors. The entrance of halogen raises the melting and boiling points and refraction and changes other physical properties in like degree.

Preparation.—1. Direct halogenation is usually successful if light and elevated temperatures are avoided, particularly if a carrier is present. If no alkyl groups are present in side-chains, the operation is easier, but in their presence there is a strong tendency to attack the aliphatic radical. As with the paraffins, iodine will not react unless some substance is added to remove the hydriodic acid that is produced.

2. The diazo reaction, involving nitrous acid on a primary amine, is useful especially for the iodide. It will be considered in detail in the next chapter, but for the present the equation may be formulated as



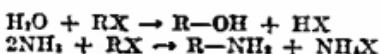
3. The chlorides may be obtained by treating the hydroxy derivative with phosphorus pentachloride, as with aliphatic alcohols, but the reaction is far from satisfactory.

4. A compound already containing halogen and a carboxy group may be heated with a caustic alkali, a method like the one used for making hydrocarbons.



Reactions.—The halogen atom is not nearly as active as that in the alkyl halides, but the presence of other substituents in the ring frequently increases the activity. With certain important exceptions, which will later be treated in detail, ammonia or caustic alkalies will not attack it easily, and warming with cyanides, metals, silver oxide, or other agents is unproductive without a catalytic agent. Indeed, it may be said in general that aryl halides are much less useful than the alkyl compounds in preparing other derivatives, although the reactions given can be carried out as noted, even if sometimes in very small yield. In case there is a reaction, its course is as we have already learned. The presence of the halogen atom makes hydrogens of the nucleus more easily substituted, since it is ortho-para-directing.

1. Caustic soda or ammonia at 200° to 300° in the presence of copper salts will give hydroxy or amino compounds. Even water at about 400° with silica gel can furnish hydroxybenzenes.



2. Alcobolates at elevated temperatures give ethers or alkoxides.



3. Treated with metals in ether solution, with or without alkyl halides, some of the aryl radicals can be coupled with others or with alkyl. This is known as the Fittig reaction and is a modification of that described by Wurtz (Chapter IV).

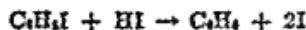


4. Some of the halides will add magnesium to produce a reactive Grignard reagent.



When such a reagent is formed, it is just as capable of adding aldehydes, ketones, cyanides, and other unsaturated compounds as if made from alkyl halides.

5. Energetic reduction with sodium amalgam or other sources of nascent hydrogen, as well as with hydriodic acid, gives inverse substitution.



When halogen is present in a side-chain, it is aliphatic and just as reactive. The chlorine atom in $\text{C}_6\text{H}_5\text{—CH}_2\text{Cl}$ could be expected to behave just as if it were in $\text{CH}_3\text{—CH}_2\text{Cl}$.

Only a few of the nryl halides are important enough to warrant special mention. Iodobenzene can be converted through chlorine and alkalies to an explosive iodosobenzene, $\text{C}_6\text{H}_5\text{IO}$, and to iodoxybenzene, $\text{C}_6\text{H}_5\text{IO}_2$, derivatives of which have been used in medicine. p-Dichlorobenzene, an aromatic solid, is sold as an insecticide and moth-repellant, sometimes under the name Dichloricide. The corresponding ortho compound is employed as cleaner and solvent. The chlorination of toluene is carried out commercially, and by regulation produces $\text{C}_6\text{H}_5\text{—CH}_2\text{Cl}$, $\text{C}_6\text{H}_5\text{—CHCl}_2$, or $\text{C}_6\text{H}_5\text{—CCl}_3$, called benzyl chloride, benzal chloride, and benzo-trichloride respectively. These and similar compounds, such as p-bromo-benzylbromide and benzyl bromide, are lachrymators and used as such, but they are chiefly of value in preparing other compounds. Polychlor derivatives of ethylbenzene are used for a number of purposes in industry, as are also similar substitution products of diphenyl.

NITRO COMPOUNDS

The nitration of paraffins in the laboratory is unimportant because not easy to promote, but in the aromatic series it is very useful. Nitric acid will attack the ring in almost every compound that has a benzene nucleus. Indeed, the reaction must be controlled by maintaining a sufficiently low temperature or it may become violent. The addition of sulfuric acid facilitates the process greatly at the necessarily low temperature and is generally adopted.



With more difficulty a second group can be introduced and also a third, but not more than three to a ring. In benzene this, according to the rule, gives chiefly m-dinitrobenzene and then sym-trinitrobenzene, $\text{C}_6\text{H}_3(\text{NO}_2)_3$.

1:3:5. Similarly, toluene yields in order 2-nitrotoluene, 2,4-dinitrotoluene, and 2,4,6-trinitrotoluene.

All of the nitro compounds are yellow liquids or crystalline solids, sparingly soluble in water, and usually volatile with steam. They are very easily decomposed, so much so that many of them explode before the boiling point is reached. Great care must be exercised, therefore, in manufacturing and handling them.

The nitro group cannot ordinarily be replaced by other radicals, but the easy reduction by nascent hydrogen to amines is one of the most useful reactions in organic chemistry, and is the only one of nitro compounds that is important. One can bring about the change by a variety of agents, such as metal and acid, hydrogen sulfide, ammonium sulfide in alcohol, electrolytic hydrogen, sodium amalgam, or stannous chloride. It is even possible to accomplish it with ordinary hydrogen at high temperature in the presence of metallic catalysts. In some of these methods it is possible to isolate several intermediate compounds, and the reduction of nitro compounds will be taken up later again. The ultimate product, however, is a primary amine derived by displacing the oxygen with hydrogen.



The influence of the nitro group on properties of other substituents is unique and sometimes remarkable. Chlorine attached to nuclear carbon is notably unresponsive to reagents, but the simultaneous presence of a nitro group renders it easily attacked. For example, 2,4-dinitrophenol is manufactured commercially by boiling 2,4-dinitrochlorobenzene with sodium hydroxide, although chlorobenzene would be altered only very slowly by the same treatment.



Nitrobenzene, $\text{C}_6\text{H}_5-\text{NO}_2$, also known as essence of mirbane, is a yellow liquid with a specific gravity of 1.2, boiling at 211° and melting at 6° . Its odor is somewhat similar to that of benzaldehyde, and its employment as a flavor for foods and beverages has caused poisonings. It is practically insoluble in water but distils easily with steam. Large quantities are produced commercially, chiefly for the preparation of aniline, but also to be used as solvent in polishes, as insecticide, and for other purposes.

The dinitrobenzenes are yellow solids, the melting points being: ortho 118° , meta 90° , para 173° . In the first the neighboring position of the substituents has such an influence that one of the groups can be replaced easily by hydroxyl using sodium hydroxide, by the amino group with ammonia, or by other radicals.

Trinitrotoluene (2,4,6), generally shortened to T.N.T., is a very important high explosive in the munitions industry, chiefly because it can only be fired by particular means and can, therefore, be used in shells. Trinitrobenzene could also be valuable as an explosive if it could be manufactured more cheaply.

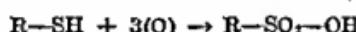
SULFONIC ACIDS

The action of sulfuric acid on aromatic compounds was found to yield sulfonic acids, $\text{R}-\text{SO}_3-\text{OH}$. These are quite analogous to the acids, $\text{R}-\text{COOH}$. They are generally named as hydrocarbonsulfonic acids, such

as benzenesulfonic or p-toluenesulfonic acid, but in complicated compounds the prefix sulfo- is sometimes used.

The compounds are soluble, hygroscopic solids with no definite melting point. Since they are residues of sulfuric acid and still contain one of its hydrogens, all of them are very strong acids. Their metallic salts are soluble generally in water, even those of barium, calcium, strontium, and lead.

The aromatic sulfonic acids are usually prepared in the direct way with sulfuric acid, often facilitated by using the fuming variety. The latter will attack benzene quickly at room temperature, while the former requires a very long time or a much higher temperature. It is possible to introduce a second and third sulfonic group, but it is very difficult to control the amounts and degree of heat in order to get a desired compound. As in the aliphatic series, they can also be obtained by oxidation of thiophenols (aryl mercaptans), R-SH, and of other sulfur derivatives.



The metallic salts are produced by heating aryl halides with sulfites.



The sulfonic acids are in themselves of minor importance, and if they are isolated it is as the metallic salts. Purification, which is not always easy, is carried out by neutralizing with lime or limestone to give soluble salts that can be separated from calcium sulfate and excess carbonate by filtration. Double decomposition with just enough sodium or potassium carbonate then gives an insoluble calcium carbonate and a solution of the sulfonate that can be evaporated.

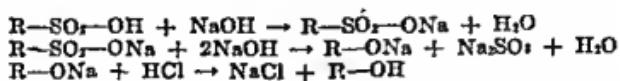
Reactions.—The sulfonic group can be altered or replaced rather easily, so that the compounds may be advantageously utilized for synthetic processes. Furthermore, the introduction of such a group leads to water-soluble substances, and this may be very convenient, especially in the field of dyes or medicinals.

1. They are strong acids and their salts are stable, as has previously been noted.

2. Heated with water or acids under pressure, they hydrolyze to reverse the method of manufacture, replacing the sulfonic group by hydrogen.



3. Fused with sodium or potassium hydroxide, they give phenates that can be converted to phenols by acidification.



4. A similar fusion with alkali cyanide gives metathesis to yield a cyanide.

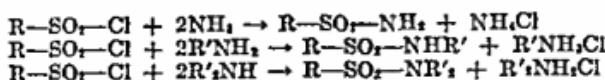


5. The sulfonic acid reduces to a sulfinic acid, R-SO₂H, and then to a thiophenol or aryl mercaptan, R-SH.

6. Phosphorus pentachloride acts upon them to replace the hydroxyl by chlorine, giving sulfonochlorides; the salts will react in the same way.



If the sulfonchlorides are boiled with dilute acid, the sulfonic acids are regenerated. With alcohols they yield alkyl sulfonates, $R-SO_2-OR'$. The most important reaction of the sulfonchlorides, however, is that with ammonia or amines, in which sulfonamides are produced.

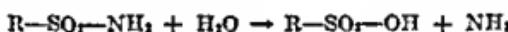


The sulfonamides show no basic character at all but, on the other hand, the proximity of the negative $-SO_2-$ renders any hydrogen of the amino group acid and replaceable by alkali metals to form soluble salts.

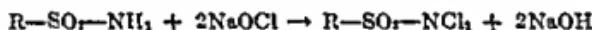


This is the basis (Hinsberg) of separating primary, secondary, and tertiary amines. The tertiary will not react with a sulfonchloride, hence can be removed from a reaction mixture. The secondary gives a product that contains no replaceable hydrogen and is not soluble in alkali. The primary amine furnishes a compound that dissolves and can be regenerated by acidifying.

The sulfonamides are decomposed by hydrolysis to the sulfonic acids, best by boiling with mineral acids.



They can also be chlorinated by hypochlorites, in which one or two of the amino hydrogens are replaced.



These sulfonchloramides slowly decompose in water to liberate hypochlorous acid, for this reason being useful antiseptics.

Benzenesulfonic acid, a very soluble solid, is sometimes employed as a substitute for sulfuric acid, chiefly because the strontium and calcium salts are soluble. m-Benzene-disulfonic acid is used similarly.

p-Toluenesulfonic acid and its primary amide are by-products in the manufacture of saccharin. The amide can be converted by sodium hypochlorite to Chloramine-T U.S.P., a salt of p-toluenesulfonchloramide, corresponding dichloride, CH_3- U.S.P., is insoluble in water and is usually dissolved in chlorinated paraffin for use.

REVIEW QUESTIONS

1. State four methods by which aryl halides may be prepared and write equations to illustrate each.
2. Why will not iodine act upon hydrogen of the benzene nucleus? How could one alter conditions to get reaction?
3. How does the reactivity of the halogen atom compare with that in alkyl halides?
4. Write equations for the action of sodium hydroxide or ammonia at high temperature, of alcohols, of metals in ether solution, including magnesium.
5. Write the formulas of benzyl chloride, benzal chloride, and benzotrichloride. How are they made?
6. Write equations for the successive nitration of toluene.
7. What is the only important chemical property of nitro compounds? Write the equation.

8. What caution must be exercised in handling the nitro compounds? What is T.N.T.?
9. State three ways for making sulfonic acids and write equations to illustrate. How are they usually made?
10. Write equations for the reactions of sulfonic acids: with alkalies in dilute solution; fused with alkalies; fused with sodium cyanide; heated with acids under pressure; with phosphorus pentachloride.
11. How do the sulfonchlorides behave with ammonia and with amines? Write equations.
12. Show how the sulfonamides behave as acids.
13. What is the product of chlorinating them? Write an equation to illustrate.
14. Write the formulas of Chloramine-T and Dichloramine-T.
15. Explain the Hinsberg method of separating primary, secondary, and tertiary amines.

CHAPTER XXVI

AMINO AND DIAZO COMPOUNDS

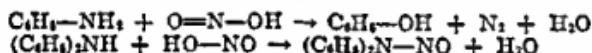
AMINES

THOSE compounds that contain primary amino nitrogen connected directly to the ring are colorless liquids or solids with a characteristic odor and sparingly soluble in water. The ones with low molecular weight will distil undecomposed and all of them are comparatively stable to heat. Like a great many aromatic compounds, they become colored rather quickly on standing and often must be redistilled alone or with steam before using.

In general the only important method for making them is from the nitro compounds by reduction. In exceptional cases that we will meet later, other functional groups can be substituted by NH₂, using ammonia or ammonium salts.

Reactions.—1. Unlike the aliphatic amines, they are relatively weak bases and are neutral to litmus. The salts are soluble in water and so easily hydrolyzed that even sodium carbonate will suffice. The secondary and tertiary compounds are even weaker than the primary, whereas the opposite condition was seen in the aliphatic amines. The presence in the nucleus of negative substituents like nitro, halogen, or hydroxy makes the basic properties still lower. Aside from the weakly basic character, however, these aromatic amines form salts and double salts that are exactly comparable to those in the chain series.

2. Nitrous acid acts on them just as it does on aliphatic amines, giving hydroxy derivatives with the primary and nitrosamines with the secondary.



The action on primary amines, however, differs sufficiently in degree to make it an extremely useful and important one, because it furnishes an easy means for preparing several classes of valuable substances. In the aliphatic series there was produced an unstable diazo compound that immediately decomposed to give the above result.



From the aromatic primary amines, the diazo compounds are stable enough to be isolated, and their reactivity with other substances makes them an important class.

The action of nitrous acid on aromatic tertiary amines is remarkably different from the aliphatic, whether only one of the three radicals is aromatic or more. Instead of merely forming a salt as we have learned, nitrous acid splits out water with hydrogen in para position to form a nitroso compound.



3. Alkylation proceeds as has already been found in the chain compounds, although the reaction is often more easily controlled because of the weaker basic character.

The three aminotoluenes or toluidines, $\text{CH}_3\text{---C}_6\text{H}_4\text{---NH}_2$, are similar to aniline in properties. The ortho compound, a liquid boiling at 201° , is a reagent of the formulary, while the para compound is a solid melting at 44° . Both turn dark on standing. The six aminoxylenes or xylidines have like properties and are sometimes used in making dyes.

Isomeric with the toluidines is henzylamine, $\text{C}_6\text{H}_5\text{---CH}_2\text{---NH}_2$, which has the odor of ammonia, is a strong base, and in general behaves like the simple alkyl amines. It can be made by the reduction of phenyl cyanide or by the action of ammonia on benzyl chloride, $\text{C}_6\text{H}_5\text{---CH}_2\text{---Cl}$. Amphetamine, N.N.R. (Benzedrine), $\text{C}_6\text{H}_5\text{---CH}_2\text{---CH}(\text{NH}_2)\text{---CH}_3$, also used as the sulfate, is like ephedrine in some respects. Although it contains an asymmetric carbon atom, the racemic form is marketed.

In Chapter XVII it was noted that long-chain quaternary ammonium salts are bactericides. Among these is Zephiran Chloride N.N.R., $\text{C}_6\text{H}_5\text{---CH}_2\text{---NR}(\text{CH}_3)_2\text{Cl}$, in which R is said to be a mixture of alkyls, C_8H_{17} to $\text{C}_{16}\text{H}_{27}$. Another is phemerol, (p-tert-octylphenoxyethoxyethyl) dimethyl-henzylammonium chloride.

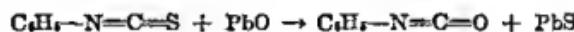
Diphenylamine, $(\text{C}_6\text{H}_5)_2\text{NH}$, an official reagent and test solution, gives an intense blue with nitric or nitrous acid. Its hexanitro compound is used as an explosive. Triphenylamine, $(\text{C}_6\text{H}_5)_3\text{N}$, is a white, insoluble solid that gives no salts with acids.

The phenylene diamines or diaminobenzenes, $\text{C}_6\text{H}_4(\text{NH}_2)_2$, are useful agents for the production of dyes. m-Phenylenediamine hydrochloride, an official reagent and test solution, gives a brown color with even a trace of nitrous acid, because of the formation of Bismarck brown.

Phenyl isocyanate, $\text{C}_6\text{H}_5\text{---N=C=O}$, is prepared from aniline through phenyl mustard oil. When aniline is treated with the vapor of carbon disulfide, as was noted before, there is formed thiocarbanilide. By heating with water, this is converted to aniline and the mustard oil.



The sulfur can then be exchanged for oxygen by heating with litharge.



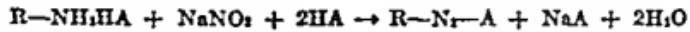
Phenyl isocyanate, a liquid whose vapors are lachrymatory, is used in the laboratory to identify alcohols, because they usually add to it to give crystalline phenylurethanes that have characteristic melting points.



In using it water must be entirely excluded, for the slightest trace gives diphenylurea, $(\text{C}_6\text{H}_5\text{NH})_2\text{CO}$.

DIAZO COMPOUNDS

The formation of a diazonium salt by action of nitrous acid on a primary aromatic amine is called diazotization. It is performed by dissolving the amine in a dilute mineral acid (HA) to form a salt, and dropping into the well cooled (about 0°) solution one of sodium nitrite.



The unstable, even explosive, diazonium salts can be preserved safely in the acid solution as long as they are kept cold but, if they are allowed to warm very much, are hydrolyzed to give phenols.



The salts can be isolated if made in non-aqueous solvents, but they are generally used for reactions in the form of the cold, dilute, aqueous solutions as produced in diazotization. This solution is called the diazo mixture or solution.

The structural formula of the diazonium salt may be expressed by $\text{R}-\text{N}=\text{N}-\text{A}$ or $\text{R}-\overset{\text{A}}{\underset{|}{\text{N}}}=\text{N}$. The latter is preferred for several reasons,



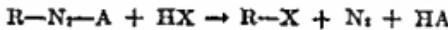
including the cogent one of electronic distribution. However, the exact structure is not practically important, and it seems entirely satisfactory to avoid any controversy by using the rational formula already given, $\text{R}-\text{N}_2-\text{A}$, at the same time noting that it is an ionic compound, $\text{R}-\text{N}_2^+ \text{A}^-$.

The salts are named as aryl diazonium, or preferably hydrocarbon diazonium, salts. Thus, $\text{C}_6\text{H}_5-\text{N}_2-\text{Cl}$ is benzenediazonium chloride or phenyldiazonium chloride, while $\text{CH}_3-\text{C}_6\text{H}_4-\text{N}_2-\text{Cl}$ 1:4 is p-toluenediazonium chloride or p-tolyldiazonium chloride.

Reactions.—The instability of diazo compounds makes them very reactive, and many processes to illustrate might be given. Those which follow are most often used in the laboratory.

1. As has already been noted, the diazo solution decomposes on warming to give nitrogen and a phenol. This is frequently a very valuable method for preparing these hydroxy compounds from amines.

2. If the mixture has been made in as concentrated a form as is consistent with stability and is then warmed with at least a molecular amount of cuprous chloride and a large excess of hydrohalogen, the halogen is found to have displaced the diazonium group.



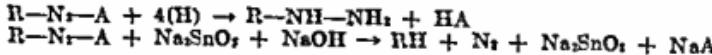
This Sandmeyer reaction constitutes the best way to introduce iodine into the ring. One can also use copper in place of cuprous chloride (Gattermann). The mechanism by which the final result is obtained is undoubtedly more complex than is indicated by the equation.

3. The Sandmeyer reaction can be modified to get a cyanide by using alkali and cuprous cyanides.

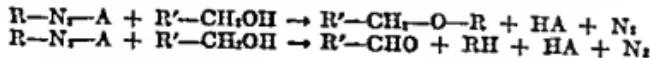


Since acids can be obtained by hydrolyzing the product, this is a convenient way to introduce carboxyl groups into the ring.

4. Reduction by stannous chloride or tin and an acid furnishes hydrazine derivatives, while basic reducing agents produce the hydrocarbon.

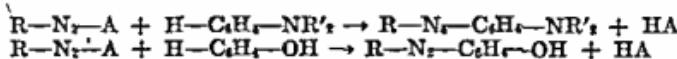


5. The hydrocarbon is also obtained, together with ether and aldehyde, by warming with an alcohol.



Which of the two reactions is predominant will depend on conditions. Neither 4 nor 5 is an important reaction of the diazo solution; they are employed only for special purposes.

6. The most useful of all reactions is the ability to couple with aromatic amines or phenols, producing an azo compound without loss of nitrogen. Essentially this is a splitting out of hydrogen para to the amino or hydroxy group with the anion of the diazonium compound.



In order to reduce the acidity of the solution, sodium hydroxide or a buffer salt is added previous to the coupling.

In the case of primary or secondary amines, the first product is a diazo amino compound. For example, aniline with benzenediazonium chloride gives diazoaminobenzene.



This can now be transformed, probably by temporary reversion to the diazonium salt, to the final azo compound by heating, especially if aniline chloride is present in excess.

The parent of these azo compounds, $\text{C}_6\text{H}_5-\text{N}_2^{\cdot}-\text{C}_6\text{H}_5$, is called azobenzene, and the substances resulting from the coupling are expressed as substitution products. The simple ones just referred to are; diazoaminobenzene, $\text{C}_6\text{H}_5-\text{N}_2^{\cdot}-\text{NH}-\text{C}_6\text{H}_5$; p-aminoazobenzene, $\text{C}_6\text{H}_5-\text{N}_2^{\cdot}-\text{C}_6\text{H}_4-\text{NH}_2$ 1:4; p-dimethylaminoazobenzene, $\text{C}_6\text{H}_5-\text{N}_2^{\cdot}-\text{C}_6\text{H}_4-\text{N}(\text{CH}_3)_2$; p-hydroxyazobenzene, $\text{C}_6\text{H}_5-\text{N}_2^{\cdot}-\text{C}_6\text{H}_4-\text{OH}$.

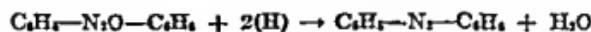
Aminoazobenzene is a yellow dye that gives highly colored salts, and will be referred to again. It can also be made by reducing the product of nitrobenzene, which is in turn prepared from nitrobenzene, as will be described.

Dimethylaminoazobenzene is used in diagnosis of free hydrochloric acid in gastric juice and will be found described as Toepfer's reagent in the Formulary. Diazobenzenesulfonic acid, made by diazotizing sulfanilic acid, is an official test solution.

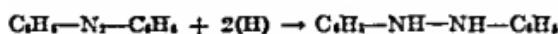
Reduction of Nitrobenzene.—When nitrobenzene is reduced with any agents, the ultimate product is aniline, but several intermediates can be obtained with some of the agents. By moderating the action in acid media, it is possible to isolate nitrosobenzene, $\text{C}_6\text{H}_5-\text{NO}$, and phenylhydroxylamine, $\text{C}_6\text{H}_5-\text{NHOH}$. With mild alkaline agents such as sodium stannite, the first product is azoxybenzene.



With the same reagents the process may be carried a step more to azobenzene.

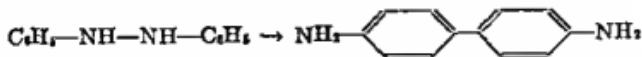


Further treatment by zinc and dilute potassium hydroxide yields hydrazobenzene.



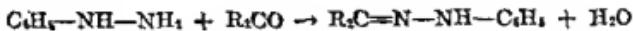
Any of these, of course, can be reduced immediately to aniline by energetic agents.

Hydrazobenzene is readily converted by action of strong acids to colorless crystals of benizidine, an official reagent.



This is an unusual rearrangement and undoubtedly involves intermediate compounds. It will be observed that benzidine is a derivative of diphenyl; indeed, it is usually made by nitrating the latter and then reducing. *o*-Tolidine, 3,3'-dimethylbenzidine, is also used as a reagent.¹

Phenylhydrazine, $C_6H_5-NH-NH_2$, and its hydrochloride and acetate, as well as 2,4-dinitrophenylhydrazine, are very useful official reagents for the identification and estimation of aldehydes and ketones by formation of phenylhydrazone.



The easy reduction of phenylhydrazine to aniline and ammonia makes it of value also in forming osazones from the sugars. The hydrochloride is sometimes used in medicine, as is also acetylphenylhydrazine, $C_6H_5-NH-NH-CO-CH_3$.

Dithizone, or diphenylthiocarbazone, $C_6H_5-NH-NH-CS-N=N-C_6H_5$, is an analytical reagent for lead.

REVIEW QUESTIONS

- How are aromatic amines made? Write the equation. How do they compare with aliphatic amines as bases?
 - How do tertiary aromatic amines behave with nitrous acid? Write equation.

(1-phenyl-2-aminopropane), diphenylamine, m-phenylene diamine, phenyl isocyanate, and phenyl mustard oil

4. How is sulfanilamide prepared? Write equations. Why will it form a sodium salt?
 5. ^{Ans} of phenyl isocyanate.
 6. an equation to illustrate.
 7. how it behaves if boiled in aqueous solution.

8. How can halides and cyanides be made by the Sandmeyer reaction? Write equations.

9. ^{e?} Write
a speci

10. phenols.

11. ^{e?} Write

12. Write formulas of diazoaminobenzene, aminoazobenzene, dimethylaminoazo-benzene, p-hydroxyazobenzene

13. Besides aniline, what other compounds can be obtained in the reduction of nitrobenzene?

14. Show how hydrazobenzene rearranges to benzidine. How is the latter usually made? Write equations.

15. Write the formulas of phenylhydrazine, acetylphenylhydrazine, 2,4-dinitrophenylhydrazine, o-tolidine, dithizone, diazobenzenesulfonic acid.

CHAPTER XXVII

PHENOOLS

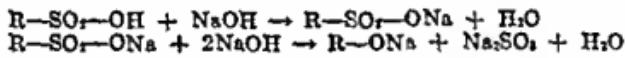
THE phenols are hydroxyl derivatives of benzene or its homologues, with the substituent connected directly to carbon of the nucleus. Therefore, they are tertiary alcohols, because the carbon atom to which the hydroxyl is attached is in turn united with other atoms of carbon only. Nevertheless, it will be found that the phenols are somewhat different in properties from tertiary alcohols of the aliphatic series.

They are usually given arbitrary names ending in -ol and indicating some natural source or other relation; cresol, thymol, resorcinol, catechol, and quinol are illustrations. Chemically the correct names designate them as hydroxy derivatives, using appropriate numbers for position.

The simple phenols or monohydroxy substitution products of aromatic hydrocarbons are crystalline solids or liquids with a characteristic odor if volatile. Some of the lower ones can be distilled readily, especially with steam, and are at least partially soluble in water. The higher ones are much less volatile and soluble. All of them dissolve easily in usual organic solvents and in aqueous solutions of caustic alkalies.

Preparation.—Several methods may be used to produce them in the laboratory, but the usual ones are the first two given.

1. The most frequent commercial process involves heating a sulfonate with a caustic base at fusion temperature.



The sodium salt that is produced is then acidified and distilled or extracted to get the phenol.

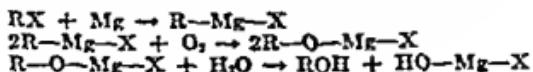


Benzenesulfonates require about 300° but some others can be converted at lower temperatures.

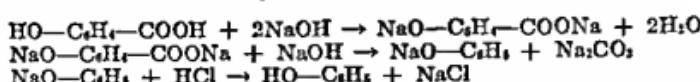
2. An aromatic primary amine can be boiled with a nitrite and a mineral acid to give the intermediate diazonium salt.



3. Halogen can be replaced by the hydroxyl group through heating with caustic alkali, although the method is very unsatisfactory unless other substituents are present in the nucleus. By means of the Grignard reaction, however, the transformation can be accomplished without difficulty, providing the aryl halide will add to magnesium. The process involves bubbling oxygen through the ethereal solution previous to hydrolysis.



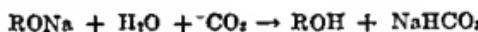
4. Substituted phenols may frequently be converted to the simple compounds by removing the other radicals. Thus, phenolic acids can be made to lose carbon dioxide by heating with sodium hydroxide.



Reactions.—1. The phenolic hydrogen is replaceable by metals to form salts, and this can be accomplished by treatment with aqueous solutions of the caustic alkalies.

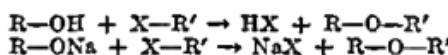


Such phenates or phenolates are soluble in water, thus making it possible to dissolve the insoluble phenols in dilute alkali. However, the phenols are very weak acids; the dissociation constant of ordinary phenol, $\text{C}_6\text{H}_5\text{OH}$, is 1.7×10^{-10} . Even such weak acids as carbonic will decompose the phenates to precipitate the phenols.



This solubility in aqueous alkali is utilized to determine the amount of phenols in official oils like that of clove. A measured amount of the oil is shaken with a dilute solution of potassium hydroxide, and the quantity of phenol is ascertained by the diminution in volume. The aqueous solution can also be separated from the residual oil and acidified, thus furnishing a means for isolating the substance.

2. Alkyl halides convert the phenols to ethers at higher temperatures, but the heat necessary is reduced if phenates are used.



The methyl or ethyl ether can usually be produced by using sulfates instead of the halides.

3. While hydrohalogen acids will not react with the hydroxyl group, phosphorus pentachloride is able to convert it to chlorine.

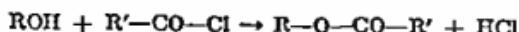


The yield is generally very low and in other ways the reaction is unsatisfactory.

4. Zinc dust at elevated temperatures removes the oxygen, an excellent means for proceeding from a phenol to the parent hydrocarbon.



5. Acid anhydrides or acid chlorides are able to esterify the phenol, but the acid itself will not usually suffice.



6. The phenols are very rapidly oxidized even by weak agents to furnish more hydroxyl groups from the nuclear hydrogen.



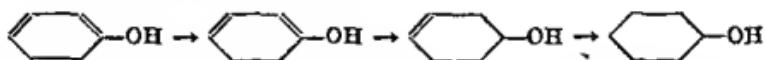
Practically all soluble phenols react with ferric chloride, probably by oxidation, to give colored compounds, and the insoluble ones give such a reaction in alcoholic solution.

7. The nuclear hydrogen of phenols is much more readily attacked than is that of the hydrocarbon. As we have already seen, it is characteristic of ortho-para-directing groups that they make easier the substitution of hydrogen by reagents. The phenols accordingly nitrate easily and react in aqueous solution with bromine; phenol itself thus forms an insoluble tribromide (2:4:6).



Nitrous acid, too, attacks the hydrogen to substitute a nitroso group, usually producing colored compounds (Liebermann reaction).

8. Reduction by the Sabatier-Senderens method with nickel at elevated temperatures and under pressure converts the phenols to hexahydrobenzene derivatives or alicyclic compounds.



This reaction is now used commercially to furnish solvents like cyclohexanol.

Phenol.—Phenol U.S.P. or carbolic acid, $\text{C}_6\text{H}_5\text{OH}$, is a colorless or pink, crystalline solid with a characteristic odor and melting at 41° to 42° . Although the boiling point is about 183° , it has a significant vapor pressure at room temperature and volatilizes easily with steam. At 25° it dissolves in 15 parts of water and also forms a homogeneous liquid with about 8 per cent of water, while at about 68° water and phenol are miscible in all proportions. Liquefied Phenol U.S.P. is about a 10 per cent solution of water in phenol. It is freely soluble in most of the organic solvents, including fixed and volatile oils. The undiluted substance cauterizes the skin and mucous membranes.

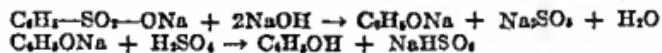
Preparation.—Until the last few years most of the phenol of commerce was obtained from coal tar, where it occurs to the extent of about 0.7 per cent, but is now made synthetically.

1. Monochlorobenzene is heated with steam at high pressure and about 400° in the presence of silica gel.



A by-product of this reaction is diphenyl ether, $\text{C}_6\text{H}_5-\text{O}-\text{C}_6\text{H}_5$, formed by a reversible reaction, so that if some of this ether is added before starting the process, an increased yield of phenol is obtained.

2. Fusion of sodium benzenesulfonate with caustic soda at about 300° gives rise to sodium phenolate, which can be decomposed by acids.



3. Phenol can be obtained by oxidation of benzene in the air in the presence of aluminum chloride or palladium.

4. In the laboratory it is sometimes made from aniline through the diazo reaction.

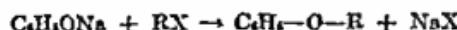


The reactions of phenol are typical of the class. With ferric chloride in neutral solution, it gives a violet color. Even in very dilute solution, bromine water produces a white precipitate of 2,4,6-tribromophenol.

bromide, $C_6H_5Br_2OBr$, easily converted by sulfites or thiosulfates to the tribromide, $C_6H_5Br_2OH$, melting at 96° . This reaction is used for identification and also as a basis for the official assay by volumetric solution of bromine. Bismuth Tribromphenate N.N.R. (Xeroform) is an insoluble compound that is used like other salts of bismuth. Sodium pentaehlorophenate is employed to preserve rubber latex.

About 50,000,000 pounds of phenol are produced annually in the United States, more than 90 per cent being synthetic. A large share of this goes to make plastics like Bakelite and for the manufacture of dyes, drugs, and photographic developers.

Ethers of phenol are prepared by heating the sodium salt with alkyl or aryl halides.



They may be reconverted to phenol by heating with hydriodic acid in strong solution.



Anisole, $C_6H_5-O-CH_3$, a liquid with pleasant odor, has been used as a delousing agent, especially in war time. Phenetole, $C_6H_5-O-CH_2-CH_3$, is similar in properties. Diphenyl ether, a by-product in manufacturing phenol from chlorobenzene, can easily be made the chief product in this process, or it may be made in other ways. It has a geranium-like odor for which it is used in perfumery. It is an excellent medium for transfer of heat and can be substituted for mercury in fluid-heating systems.

The esters of phenol are easily hydrolyzed unless not very soluble. The most important is salol which will be considered later.

The nitro derivatives are much more acidic than phenol and not very soluble in water. Direct action of dilute nitric acid at less than room temperature and subsequent distillation produces a distillate of the ortho and a residue of the para. The meta can be made by diazotizing m-nitraniline.



Dinitrophenol (2:4) is manufactured by the action of dilute nitric acid and mercurous nitrate on benzene.



It is a yellow, crystalline compound that is about as strong an acid as formic; dissociation is 1×10^{-4} . It is efficient in reducing weight in the obese by increasing metabolism and temperature, but it is said to be very dangerous.

Trinitrophenol.—Trinitrophenol U.S.P. (Picric Acid), $C_6H_5(OH)(NO_2)_2$, 1:2:4:6, is produced by nitration of benzene in the presence of mercurous nitrate or of phenol at 100° . It can be made also by nitration of silk, wood, many resins, and numerous other natural materials. Picric acid is a yellow, crystalline substance that is explosive when dry but stable if incorporated with some water. It is only sparingly soluble in cold water but is more soluble in hot water or in alcohol, and these solutions dye silk or wool. The dissociation constant is about 1.6×10^{-5} , making it about as strong as acids like hydrochloric. The potassium salt is sparingly soluble and can be used for the identification of the metal. Silver Picrate N.N.R. is used like other silver salts. Picric acid forms precipitates with many

alkaloids, often an excellent means to distinguish them, and molecular addition products with many complex hydrocarbons. Chlorine or bleaching powder oxidizes it to nitrochloroform or chloropicrin, CCl_3NO_2 , a commercial insecticide.

The simple amino derivatives of phenol are important as dye intermediates. Since they are both acids and bases, due to the hydroxyl and amino groups, they will form unstable salts with alkalies or mineral acids. They are especially easily oxidized and often used as reducing agents, particularly for developing photographic exposures.

· Paraminophenol might be prepared by reduction of the nitro compound, but is usually made by electrolytic reduction of nitrobenzene.



The rearrangement of the first product, phenylhydroxylamine, to p-aminophenol is similar to those of hydrazobenzene to benzidine (Chapter XXVI) and of methylaniline to aminotoluene. The hydrochloride of p-aminophenol is sold as Rodinol and the sulfate of its methylated derivative as Metol, both useful developers. Other developers of similar kind are: o-methylaminophenol, Ortol; 2,4-diaminophenol dihydrochloride, Amidol; and p-aminosaligenin, $\text{C}_6\text{H}_5(\text{OH})(\text{CH}_2\text{OH})\text{NH}_2$, 1:2:4, Edinol.

Tyramine, $\text{H}_2\text{N}-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{NH}_2$ 1:4, occ. It is more basic than p-aminophenol and is sometimes used like epinephrine in medicine as the hydrochloride.

Sulfonation of phenol in the cold yields chiefly o-phenolsulfonic acid, but when warm the para compound. Furthermore, the former will rearrange to the latter upon heating, showing that it is less stable. Salts of p-phenolsulfonic acid are used as antiseptics, often under the title of sulfocarholates. Zinc Phenolsulfonate N.F. is marketed in soluble crystals that contain 8 molecules of water. An official reagent called phenoldisulfonic acid is an indefinite mixture prepared from phenol and reagent sulfuric acid.

Cresol.—Cresol U.S.P. is a mixture of the three hydroxytoluenes, $\text{CH}_3-\text{C}_6\text{H}_4-\text{OH}$. They are found in coal, wood, and pine tar and in other products of destructive distillation. The ortho compound is contained as the sulfate in the urine of horses, the para in human urine. All of them are sparingly soluble in water but dissolve readily in strong alkalies, not in carbonates. They give a bluish color with ferric chloride and reduce with zinc to toluene. Saponated Solution of Cresol U.S.P. (Compound Solution of Cresol) is a very common antiseptic; commercial Lysol is essentially the same. Cresatin N.N.R., a liquid antiseptic, is the acetate of m-cresol.

Metaphen N.N.R., another antiseptic, is described as the anhydride of 4-nitro-5-hydroxymercuri-o-cresol. A number of other mercurials in which the metal is connected directly to the ring have been introduced into medicine. The connection to carbon can be effected in a variety of ways: directly by heating with mercuric salts; through the Grignard reaction; by displacement of the carboxyl group by the diazonium salt. Merphenyl Nitrate N.N.R., Merphenyl Borate N.N.R., and Merphenyl Picrate N.N.R.

Tri-o-cresyl phosphate is very commonly used in the manufacture of polishes, varnishes, lacquers, and plastics. It was responsible several years

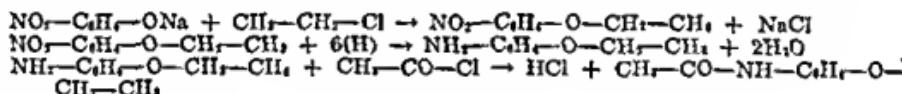
ago for the many cases of "jake" paralysis that were caused by drinking adulterated preparations of Jamaica ginger.

Thymol.—Thymol U.S.P., $\text{CH}_3-\text{C}_6\text{H}_4(\text{OH})-\text{CH}(\text{CH}_3)_2$, 1:3:4, might be described as 3-hydroxy-4-isopropyltoluene or 2-isopropyl-5-methylphenol. It consists of aromatic, colorless, insoluble crystals melting at 51.5° . It can be obtained from the official oil of thyme and from many other oils, or it can be made synthetically from cymene. Determination of the amount in oils is made by noting the volume that dissolves in dilute alkali. In alcoholic solution thymol produces a green color with ferric chloride, but none in water because of its insolubility. Thymol Iodide U.S.P. (Aristol), obtained by the action of iodine on thymol, is insoluble in water and is used as a substitute for iodoform. Chlorothymol N.F. is employed in medicine like thymol.

Carvacrol, isomeric with thymol, has the formula $\text{CH}_3-\text{C}_6\text{H}_4(\text{OH})-\text{CH}(\text{CH}_3)_2$, 1:2:4. It also is found in many of the volatile oils and is sometimes the chief constituent. Several similar phenols are commercial solvents and intermediates in the preparation of plastics; among them might be mentioned p-tert-butylphenol and p-tert-amylphenol (Pentaphen).

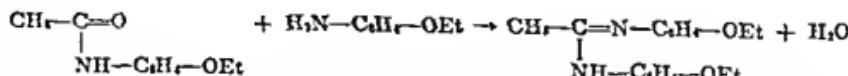
Anethol.—Anethol N.F. (Anethole), p-methoxypropenylbenzene, $\text{CH}_3-\text{O}-\text{C}_6\text{H}_4-\text{CH}=\text{CH}-\text{CH}_3$, 1:4, is the chief ingredient of the oils of anise and fennel. It is not soluble in alkalies, because it is not a phenol but the methyl ether of a phenol called isochavicol, $\text{HO}-\text{C}_6\text{H}_4-\text{CH}=\text{CH}-\text{CH}_3$. The isomeric allyl compound, chavicol, $\text{HO}-\text{C}_6\text{H}_4-\text{CH}_2-\text{CH}=\text{CH}_2$, is an ingredient of hay oil. Its methyl ether, isomeric with anethol, is obtained from esdragon oil.

Acetophenetidin.—Acetophenetidin U.S.P. (Phenacetin), $\text{CH}_3-\text{CH}_2-\text{O}-\text{C}_6\text{H}_4-\text{NH}-\text{CO}-\text{CH}_3$, 1:4, is the ethoxy derivative of acetanilide, and used in the same way. The sodium salt of p-nitrophenol is heated with ethyl chloride to form the ether which is then reduced and acetylated.



It is easily hydrolyzed to p-phenetidine, $\text{NH}-\text{C}_6\text{H}_4-\text{O}-\text{CH}_2-\text{CH}_3$. Lactophenin or lactylphenetidine, $\text{CH}_3-\text{CH}_2-\text{O}-\text{C}_6\text{H}_4-\text{NH}-\text{CO}-\text{CHOH}-\text{CH}_3$, has likewise been used in medicine. The similar carhamyl compound, $\text{Et}-\text{O}-\text{C}_6\text{H}_4-\text{NH}-\text{CO}-\text{NH}_2$, is a sweet substance known as dulcin or sucrol.

Phenacaine Hydrochloride.—Phenacaine Hydrochloride U.S.P. (Holocaine Hydrochloride) is important as a local anesthetic, particularly in ophthalmology. It is manufactured by the condensation of aceto-phenetidine and p-phenetidine.

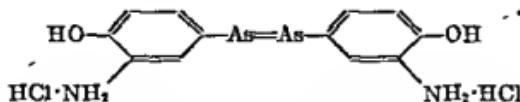


Diethylstilbestrol U.S.P., 3,4-di-p-hydroxyphenyl-3-hexene, $\text{HO}-\text{C}_6\text{H}_4-\text{C}(\text{Et})=\text{C}(\text{Et})-\text{C}_6\text{H}_4-\text{OH}$, is a synthetic substance with estrogenic action. Another compound that is similar is Octofolin N.N.R., 2,4-di-p-hydroxyphenyl-3-ethylhexane.

ARSENICALS

The important compounds of arsenic that are used in medicine are phenolic, and others are included for convenience.

Arsphenamine.—Arsphenamine U.S.P. (Arsenobenzol, Diarsenol, Salvarsan, 606),



is manufactured from phenol. This is first arsenated by beating with arsenic acid in a process analogous to nitration.



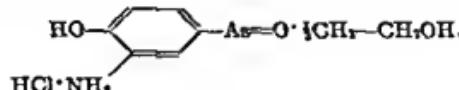
It will be noted that the product is an arsonic acid, specifically p-hydroxybenzenearsonic acid. This is now nitrated in the usual way, resulting in a nitro group ortho to the hydroxyl and meta to arsenic. Treatment with sodium hydrosulfite reduces this to amino and the arsenic to the equivalent of an azo linkage. The chemical name is derived by giving the title of arsenobenzene to $\text{C}_6\text{H}_5-\text{As}=\text{As}-\text{C}_6\text{H}_5$. It then becomes 3,3'-diamino-4,4'-dihydroxyarsenobenzene dihydrochloride.

Arsphenamine is precipitated by alkalies because its free amino base is insoluble in water, but it dissolves in excess to form a phenate, the usual form of injection. The sodium salt is sometimes marketed, also Silver Arsphenamine N.N.R. All of these compounds are easily oxidized in the air to become more toxic and should be used immediately after opening the sealed containers.

Neoarsphenamine.—Neoarsphenamine U.S.P. (Novarsenobenzol, Neodiarsenol, Neosalvarsan) is a derivative of arsphenamine by replacing one hydrogen of an amino group by $-\text{CH}_2-\text{O}-\text{S}-\text{ONa}$. The chemical name is sodium 3,3'-diamino-4,4'-dihydroxyarsenobenzene-N-methanalsulfoxylate. It is soluble in water and is used by injection without any addition. However, it also is unstable in the air and should be injected immediately after opening the ampul.

Sulfarsphenamine.—Sulfarsphenamine N.N.R. is an analogous disodium salt of a compound containing $-\text{CH}_2-\text{SO}_2\text{OH}$ in place of one hydrogen in each amino radical. It is disodium 3,3'-diamino-4,4'-dihydroxyarsenobenzene-N-dimethylenesulfonate. Bismarsen N.N.R. is the bismuth salt.

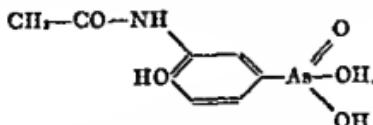
Oxophenarsine Hydrochloride U.S.P. (Mapharsen) is 4-hydroxy-3-amino-phenylarsine oxide hydrochloride with alcohol of crystallization,



The corresponding dichloro compound is described as Dichlorophenarsine Hydrochloride U.S.P.

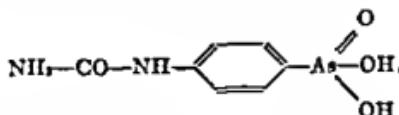
Among the first arsenicals to be made for medicinal use were substituted arsonic acids and their salts, and new ones have been more recently introduced. Atoxyl, the sodium salt of p-aminophenylarsonic acid, $\text{NH}_2-\text{C}_6\text{H}_4-\text{AsO(OH)}\text{ONa}$ 1:4, and the corresponding acetyl derivative, arsacetin, were among the first.

Acetarsone.—Acetarsone N.N.R. (Stovarsol), 3-acetamino-4-hydroxyphenylarsonic acid,



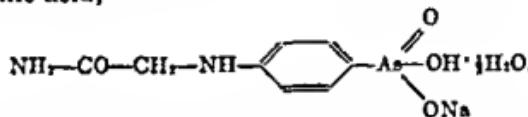
is used orally in children for arsenical treatment.

Carbarsone.—Carbarsone N.N.R. is p-carbamylphenylarsonic acid,



It is chiefly applied in amebiasis.

Tryparsamide.—Tryparsamide U.S.P., the sodium salt of N-phenylglycinamide-p-arsonic acid,



is employed against trypanosomes and spirochetes. Phenarsone Sulfoxylate N.N.R. (Aldarsone) is a similar salt.

Many compounds of antimony with structure similar to arsphenamine and arsonic acids have been made, and several are used in medicine. There may be mentioned stibosan, stibamine, stibenyl, neostam, and Fuadin N.N.R. (Stibophen).

REVIEW QUESTIONS

1. What is a phenol? To what class of alcohols does it belong?
2. State four methods for making phenols and write an equation to illustrate each.
3. How can a phenol be converted to a phenate? What is the effect of carbonic acid on solutions of phenates? Write equations for each reaction.
4. Write equations to show conversion of phenols to ethers, aromatic chlorides, the hydrocarbon, esters.
5. Why are phenols reducing agents? What is the action with ferric chloride?
6. What happens to a phenol on heating?
7.
8.
9.

phenol, picric acid, zinc phenol-sulfonate, paraminophenol.

10. How does picric acid compare with the mineral acids in strength? Why is it mixed with water?

11. Write the formulas of the three cresols, tri-o-cresol phosphate, thymol, anethole, carvacrol, mephenyl nitrate

12. How is the amount of a phenol in volatile oils determined?

13. How is acetophenetidine made? phenacetine? Write equations for the processes.

14. Show by means of equations what happens to a phenol when it is heated up to an excess?

15. What happens to it when it is heated up to an excess?

Why must it be used immediately?

16. Write the formulas of neoxarsphenamine, an arsonic acid, tryparsamide, oxo-phenazine, carbarsone, acetarsone, diethylstilbestrol

CHAPTER XXVIII

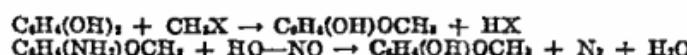
POLYHYDRIC PHENOLS

THE presence of more than one hydroxyl group connected to carbon of the ring renders the compound soluble in water and increases its reducing properties. Otherwise such compounds are like the simple phenols, although they can be esterified more than once and each hydroxyl can be made into an ether separately. They are weak acids and give colors with ferric chloride.

All three of the dihydroxyhenzenes are important substances. Two of them can be obtained from natural materials, but it is easy to devise synthetic methods of preparation for each one. For example, the ortho and para isomers will be produced if one starts with phenol and introduces another group that can be changed to hydroxyl, such as sulfonic acid. On the other hand, the normal product of nitrating benzene or nitrobenzene, m-dinitrobenzene, will furnish m-dihydroxybenzene if reduced and diazotized.

Catechol or pyrocatechin, o-dihydroxybenzene, occurs in raw beet sugar and in the leaves and sap of some plants. It is evolved by the dry distillation of several resins, including catechu which gives its name to the compound. In the laboratory it may be prepared by: heating o-chlorophenol with potassium hydroxide in the presence of copper sulfate; fusing sodium o-phenolsulfonate with sodium hydroxide; or heating guaiacol with hydriodic acid. The colorless, soluble, crystalline product gives a green color with ferric chloride and reduces silver nitrate or Fehling's solution. When exposed to the air, its alkaline solution turns green and then black by absorption of oxygen. The chief interest in catechol lies in its use for the synthesis of epinephrine and in several derivatives that are used in medicine.

Guaiacon.—Guaiacon N.F., chemically methylcatechol, o-methoxyphenol, or o-hydroxyanisole, is the chief ingredient of creosote from the distillation of wood, but can be obtained from guaiac resin, from which it gets its name. Synthetically it may be prepared by methylating catechol or diazotizing o-anisidine.



Guaiacon is a heavy, insoluble liquid with a pleasant odor and melting at 28°. The crystalline substance, once melted, does not solidify readily on cooling. With ferric chloride in alcoholic solution it gives a blue color changing to green and finally yellow. It is converted to catechol by boiling with hydriodic or hydrochloric acid. Several esters have been introduced into medicine at one time or another, but the only one official is Guaiacon Carbonate N.F. (Duotal), $\text{CH}_3\text{O}-\text{C}_6\text{H}_4-\text{O}-\text{CO}-\text{O}-\text{C}_6\text{H}_4-\text{OCH}_3$, an insoluble powder. Potassium Guaiacon Sulfonate N.F. (Thiocol), $\text{C}_6\text{H}_3(\text{OH})-(\text{OCH}_3)\text{SO}_3\text{OK}$ 1:2:6, was introduced to get the effects of guaiacol in soluble form.

Creosote.—Creosote N.F. is a mixture of phenols obtained by the destructive distillation of wood, generally beech. It contains about 60 per cent of guaiacol and a large share of the rest is the homologous creosol, 4-hydroxy-3-methoxytoluene. Creosote Carbonate N.F., a mixture of the carbonates of the various constituents of creosote, and Calcium Creosotate N.F. (Calereose), a partly soluble mixture of the calcium salts, are used like guaiacol and creosote.

The destructive distillation of other natural substances furnishes tarry materials that contain large amounts of phenols and are used in medicine on this account. Juniper Tar U.S.P. is an oily substance obtained from the wood of *Juniperus Oxycedrus L.* and was formerly official as oil of cade. Pine Tar U.S.P., from the wood of common pines, is very similar. Coal Tar N.F. and White Pine N.F. are probably dependent for value in therapy on the phenols contained.

The dimethyl ether of catechol is known as veratrole. It can be obtained from guaiacol or from catechol by treatment with dimethyl sulfate and sodium hydroxide.

Resorcinol.—Resorcinol U.S.P., m-dihydroxybenzene, consists of colorless, soluble crystals that melt at 109° to 111° . It can be produced by heating many ortho, meta, and para compounds with potassium or sodium hydroxide, showing a shift in position and indicating that meta is the most stable form. Commercially the most useful process for manufacture is the fusion of sodium benzenedisulfonate with sodium hydroxide; the former is made by the direct sulfonation of benzene. A laboratory method consists in diazotization of m-diaminobenzene, obtainable from benzene by nitration and reduction.

A solution of resorcinol is colorless but quickly turns yellow to brown by absorption of oxygen, and this change goes on much more readily if alkali is present. It is strong enough in reducing properties to affect Fehling's solution but is weaker in this respect than catechol. With ferric chloride it gives a blue color that turns brown-yellow on the addition of ammonia, a distinction from catechol and quinol. Heated with zinc chloride and phthalic anhydride, it is converted to fluorescein, and with sodium nitrite and heat forms the blue dye lacmoid.

Resorcinol Monoacetate N.N.R. (Euresol) is made by acetylation. Hexylresorcinol U.S.P. contains a normal hexyl radical in position 4, ortho and para to the two hydroxyls. It is used somewhat as an antihelmintic, often under the title of Caprokol, and as an antiseptic solution under the name S.T.37; it is claimed to reduce the surface tension in aqueous solutions to 37 dynes per square centimeter.

Resorcinol itself, besides being used in medicine, is considerably applied in industry for the manufacture of dyes, explosives, and various organic chemicals, also in tanning, textile printing, and many other ways.

Orcinol or homoresorcinol, $C_6H_3(OH)_2CH_3$, 1:3:5, an official reagent, is related to litmus and is found in many other plants, particularly the lichens. It can be prepared from aloë by heating with potassium hydroxide.

Hydroquinone or quinol is the paradihydroxybenzene, corresponding to catechol (ortho) and resorcinol (meta). It is found in the glucoside arbutin of urn tree and several other plants of the Ericaceae, and is produced by dry distillation of quinic acid, an alicyclic compound, or other natural materials. In the laboratory it can be made by the oxidation of either

aniline or pbenol with chromic acid and subsequent reduction by sulfurous acid or nascent hydrogen.

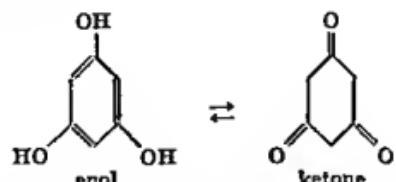
Quinol consists of colorless, soluble crystals that melt at 170° to 171° and sublime unchanged. It is very easily oxidized to quinone and, hence, a useful developer in photography. Ferric chloride consequently gives such an oxidation and not a color as with other pbenols.

All three of the trihydroxybenzenes are known but only two warrant any discussion. The other (1:2:4) is known as hydroxyquinol because oxidation of quinol to form another hydroxyl group can lead only to this compound.

Pyrogallol.—Pyrogallol N.F. (Pyrogallic Acid), $C_6H_3(OH)_3$, 1:2:3, is a product of heating gallic acid, giving the name, and so is obtainable from many tannins, including the official tannic acid. It forms colorless, soluble crystals that melt at 130° to 133°, sublime easily, and turn grayish on exposure to air and light. It is a much stronger reducing agent than the dihydroxybenzenes and is easily oxidized by silver nitrate or Fehling's solution. An aqueous solution rapidly turns brown in the air while an alkaline solution darkens even more quickly. This reaction can be used to measure the amount of oxygen in air or in a gas mixture because the absorption is reliable and complete. Ferric chloride gives a brownish-red color, but a mixture of ferric and ferrous salts produces a dark blue. An aqueous solution of pyrogallol reduces solutions of the salts of silver, gold or mercury in the cold. Furthermore, the reducing action of pyrogallol is the explanation for its use in medicine. Lenigallol N.N.R., the triacetate, is used in the same way but has the advantage of slowly liberating the phenol to give prolonged action.

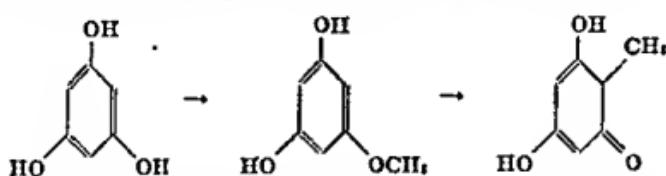
Phloroglucinol, $C_6H_3(OH)_3$, 1:3:5, an official reagent, can be prepared by heating any of numerous substances with potassium hydroxide. These include pbenol, resorcinol, orcinol, tannins, and resins like gamboge; it receives its name from the glycoside, phlorizin. The commercial method of manufacture is by fusing resorcinol with potassium hydroxide. It consists of colorless crystals that melt at 216° to 219° if heated rapidly, and is peculiarly not very soluble in water. It is a strong reducing agent but not as much so as pyrogallol. Its aqueous solution gives a violet color with ferric chloride. A most interesting reaction is with furfural giving a black precipitate.

Some of the abnormal actions of phloroglucinol are undoubtedly explained on the basis of a tautomeric mixture. Although no one has ever isolated the isomeric forms, there seems little doubt that they exist in equilibrium according to the equation:



As evidence for the enol formula, phloroglucinol will form metallic salts, a trimethyl ether that is insoluble in alkalies, and a triacetate by acetylation. On the other hand, in many of its reactions we find the behavior of a ketone; for example, it forms a trioxime and, when alkylated in the

presence of alcoholic potash, the alkyl groups go to carbon instead of oxygen, just as was the case with acetoacetic ester and malonic ester. In this way a total of six alkyl groups can be introduced.

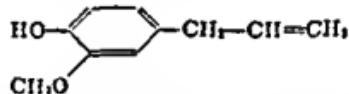


This abrupt and reversible change to alicyclic structure will be encountered again.

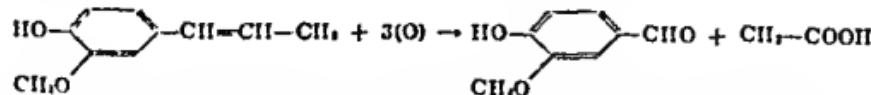
Filicin of the official aspidium and the related filicic acid are derivatives of the ketone formula of phloroglucinol.

In many of the volatile oils are found phenols or their ethers derived from allylbenzene, $C_6H_5-CH_2-CH=CH_2$, or of its isomer propenylbenzene, $C_6H_5-CH=CH-CH_3$. The usual form contains the allyl group, but this can readily be converted by heating with alkali to the more stable propenyl group. Compounds containing the latter are designated as iso derivatives of the allyl form. Thus, as we have already seen in the last chapter, the simplest one of the series from oil of bay, p-allylphenol or $HO-C_6H_4-CH_2-CH=CH_2$, is known as ephavieol, while p-propenylphenol or $HO-C_6H_4-CH_2-CH=CH-CH_3$, is isoephavieol. Methylephavieol from esdragon oil, p-methoxynallylbenzene, is isomeric with anethole which might also be called isomethylephavieol.

Eugenol.—Eugenol U.S.P., 3-methoxy-4-hydroxyallylbenzene, or

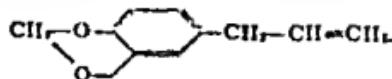


is the chief constituent of the oils of clove, pimenta, and bay leaf and is found in many others. It is a heavy, colorless liquid that boils at 250° to 255° and is only sparingly soluble in water. Being a phenol, it is soluble in fixed alkalies, and gives a transient grayish color with ferric chloride. Determination of amount in the oils depends upon the diminution in volume when shaken with a dilute solution of potassium hydroxide. When eugenol is heated with alcoholic alkali, it is converted to the stable isoeugenol which is also a constituent of clove oil. Oxidation of isoeugenol splits the compound at the double bond to give vanillin and acetie acid.



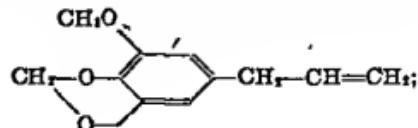
Methyleugenol and methylisoeugenol are likewise found in this and other oils, as in eugenol acetate or acetyleugenol.

Safrole is the methylene ether of the corresponding dihydroxyallylbenzene,

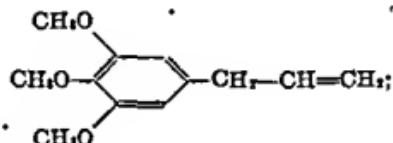


It is the chief constituent of official sassafras oil. It can be converted to isosafrole which also occurs in the oil. Upon oxidation isosafrole is changed to an aldehyde, piperonal, a reaction similar to the formation of vanillin from isoeugenol.

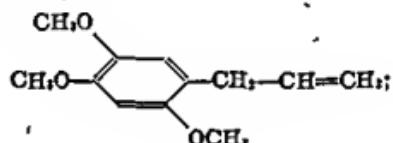
Other ethers of this series and the corresponding iso compounds are of less importance. The formulas of a few of the allyl compounds are given, together with the names of oils in which they are found: myristicin from oil of nutmeg,



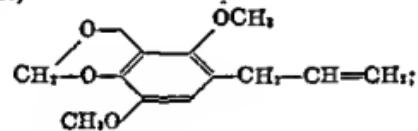
elemicin from oil of elemi,



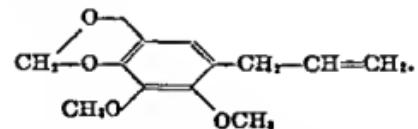
asarone from oil of wild ginger,



apiol from celery fruit,



and dill apiole from oil of dill,



REVIEW QUESTIONS

- How do the polyhydric phenols compare with simple phenols in solubility, acidity, and reducing power?
- From what does catechol receive its name? How can it be prepared in the laboratory? Write equations.
- What is the source of guaiacol? How is it made in the laboratory? Write equations.
- What is the difference in the two forms of guaiacol?
- How can it be converted to catechol? Write equation.
- Write formulas of guaiacol carbonate and potassium guaiacolsulfonate.
- Name and write the formulas of the two chief constituents of creosote. What is calcium creosotate?
- Write the equation for the commercial production of resorcinol. Why can it be made from o-hzenenedisulfonic acid by fusing with sodium hydroxide?

9. Write equation for preparation of hydroquinone. Why does ferric chloride give no color with it?
10. Write the formula of pyrogallol. How is it used in gas analysis?
11. How is phloroglucinol made from resorcinol? Write the equations. How does it differ in solubility from the other polyhydric phenols?
12. Show the tautomerism of phloroglucinol and state two reasons to think this takes place.
13. Write formulas of eugenol, isoeugenol, methyleugenol, methylisoeugenol, eugenol acetate, safrole.
14. How is the amount of eugenol in an oil determined?
15. Name three other allyl phenol ethers found in volatile oils.

CHAPTER XXIX

AROMATIC ALCOHOLS

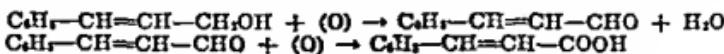
ACTUALLY the only aromatic alcohols are phenols which we have just considered in detail. Any other compounds containing the benzene nucleus and a hydroxyl group must have the latter connected to a carbon atom in a side-chain and would naturally have the properties of aliphatic alcohols. For that reason it is entirely unnecessary to give an extended discussion of them, and we could reasonably dismiss them in a volume devoted to essentials were it not for the fact that several useful therapeutic agents belong in this class.

Benzyl Alcohol N.N.R. (Phenylcarbinol), $C_6H_5CH_2OH$, occurs widely in volatile oils and balsams, often in the free state but usually as ester. It is a difficultly soluble, heavy liquid with a faint pleasant odor and its boiling point is about 205° . It is prepared commercially by boiling benzyl chloride with lime, potash, or litharge, but can be made from benzaldehyde by reduction with nascent hydrogen or by the Cannizzaro reaction (Chapter XXX). The primary alcohol group reacts like the same group in its aliphatic relatives, except in degree; concentrated hydrochloric acid converts it easily to the chloride, whereas alkylcarbinols require stronger agents. Benzyl alcohol is a local anesthetic, and its esters are used in perfumery.

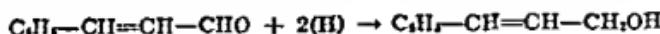
Pbenylethyl alcohol, $C_6H_5-CH_2-CH_2OH$, also a local anesthetic, is a liquid boiling at about 220° . It is found in several oils, particularly in that of rose. Although it is neither the characteristic constituent of the latter nor the ingredient in largest amount, yet it is often called rose oil. Its esters are used in perfumery. Pbenylpropyl alcohol, $C_6H_5-CH_2-CH_2-CH_2OH$, similarly is anesthetic and is found in some ethereal oils.

Salicyl alcohol or saligenin, o-hydroxybenzyl alcohol, $HO-C_6H_4-CH_2OH$ 1:2, is obtained by hydrolysis of Salicin N.F. or by heating phenol with methyl chloride and sodium hydroxide. It is a colorless, crystalline solid melting at 82° . Having the nuclear hydroxyl, it is a phenol and, as such, gives a blue color with ferric chloride and reacts with bases to form salts. It is frequently added to drugs that are designed for injection because of its local anesthetic effect, as in Iodobismitol with Saligenin N.N.R. It is interesting to note that salicyl alcohol is one of the first products of heating formaldehyde and phenol with caustic alkali in the manufacture of bakelite.

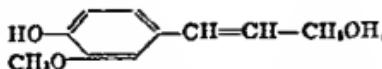
Cinnamyl alcohol, $C_6H_5-CH=CH-CH_2OH$, occurs in the free state and as esters in several oils and especially balsams such as storax, where it exists as the ester of cinnamic acid. The alcohol has an odor of hyacinth that makes it valuable in perfumery. It reduces with nascent hydrogen to phenylpropyl alcohol (hydrocinnamyl alcohol). Oxygen in the presence of platinum black converts it to cinnamic aldehyde, while chromic acid carries the process a step farther to cinnamic acid.



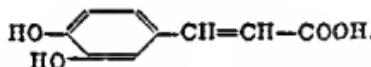
In commerce the alcohol is prepared by reducing cinnamic aldehyde by means of aluminum isopropylate.



Coniferyl alcohol,



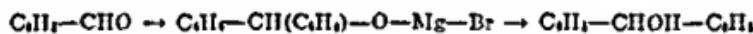
may be regarded as hydroxyisoeugenol or also as 4-hydroxy-3-methoxy-cinnamyl alcohol. It is closely related to lignin and is found in the glycoside, coniferin, of the sap in conifers and other trees. From this compound it may be obtained by hydrolysis. Oxidation of coniferyl alcohol in such a way as to split the double bond yields vanillin, analogous to the process by which the latter is obtained from isoeugenol. This oxidation is fast becoming very important as utilization for sulfite waste in the manufacture of paper. It is interesting to observe that caffic acid is the corresponding diphenolic acid,



Diphenylcarbinol, $(\text{C}_6\text{H}_5)_2\text{CHOH}$, a solid melting at 68° , can be made by reducing the corresponding ketone, benzophenone, or by oxidizing diphenylmethane.



The action of benzaldehyde and phenylmagnesium bromide furnishes another method.

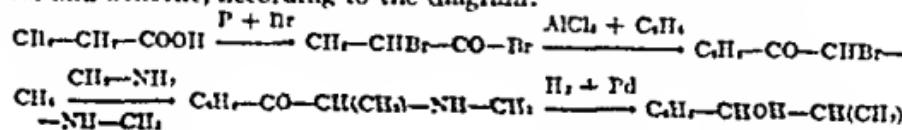


The alcohol is easily reoxidized to benzophenone.

Triphenylcarbinol, $(\text{C}_6\text{H}_5)_3\text{COH}$, can be obtained in like manner from triphenylmethane. It is closely related to a number of dyes and will be considered again. Hydrohalogens very easily react to form the chloride, as does also acetyl chloride which might have been expected to acetylate the hydroxyl group to furnish an acetate, $(\text{C}_6\text{H}_5)_3\text{C}-\text{O}-\text{CO}-\text{CH}_3$.

Ephedrine U.S.P., $\text{C}_6\text{H}_5-\text{CHOH}-\text{CH}(\text{CH}_3)-\text{NH}-\text{CH}_3$, was originally found in the Chinese drug, MaHuang. Being an amine and thus possessing the ability of forming salts with acids, it is usually classed with the alkaloids. Owing to a variable quantity of water contained in its molecule, ephedrine does not show a constant melting point, which is roughly between 34° and 40° . The alkaloid is frequently employed also in the form of its sulfate and hydrochloride, both of which are official.

The formula of ephedrine contains two nonsymmetric carbon atoms and, hence, can represent four compounds, two dextro and two levo. The natural substance is levo, and the corresponding dextro form possesses much less physiological activity. Racephedrine N.N.R., the racemic mixture of these, was made possible by the synthesis in 1920 from propionic acid and benzene, according to the diagram:



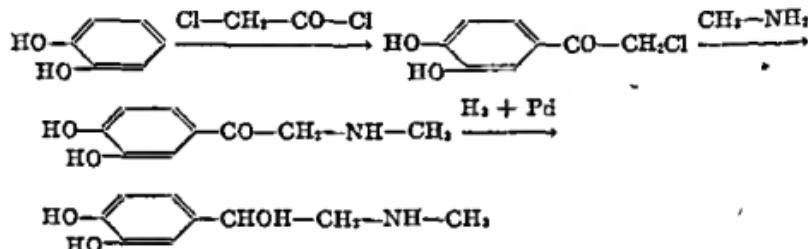
The racemic compound thus produced can be resolved into the active levo form and the less active dextro form. The sulfate and hydrochloride are employed like the salts of ephedrine.

The most interesting reaction of ephedrine is its ability to hydrolyze chloroform. If a solution in this solvent is evaporated to dryness, crystals of the hydrochloride appear as a residue. To be noted also is the fact that ephedrine is strong enough as a base to turn moistened litmus blue.

Epinephrine U.S.P. (Adrenalin, Suprarenalin, 1-l-methylaminoethanol-catechol, 1(3,4-dihydroxyphenyl)-2-methylaminoethanol),



is the extremely powerful hormone of the suprarenal medulla. It was isolated in 1901, and the structure was established and confirmed by synthesis a few years later. The process, similar to that for ephedrine but starting with catechol in place of benzene, is here shown diagrammatically:



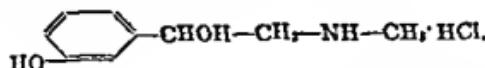
The product from this process is the racemic form and must be resolved into the optically active components, because the dextro variety possesses but a small fraction of the physiological potency inherent in the levo. Suprarenin is one brand name for the racemic material, used as Suprarenin Bitartrate N.N.R.

Epinephrine is practically insoluble in water but is a nitrogenous base and, therefore, dissolves in dilute acids. On the other hand, being a phenol it dissolves in fixed alkalies. From acid solution the free base is precipitated by the addition of ammonia or carbonates, but not by sodium or potassium hydroxide. Because of the phenolic character, the base or its salts give with ferric chloride an emerald-green color, changing to cherry-red and finally brown. Also like other phenols, it is very unstable to oxygen or oxidizing agents; indeed, its solution cannot be retained in the air very long without losing practically all of its strength, and the physiological action although powerful is quite transitory.

Owing to the great importance of ephedrine and epinephrine in medicine, chemists have prepared hundreds of compounds that are similar to them in structure in attempts to discover something better, or at least as good. While the purpose has not been accomplished in so far as epinephrine is concerned, yet several substances have been introduced into medicine that have had some use. We have already referred to benzedrine and tyramine, both of which resemble these two compounds in structure. In spite of the fact that some of the newer remedies are almost identical in chemical constitution, none has been found that even approached epinephrine in potency.

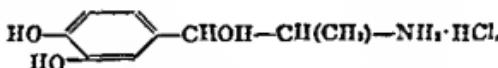
Phenylaminoethanol, $C_6H_5\text{—CHOH—CH}_2\text{—NH}_2$, was one of the first but has now been dropped. Propadrine Hydrochloride N.N.R. is the salt of a homologue, $C_6H_5\text{—CHOH—CH(CH}_3\text{)—NH}_2\text{·HCl}$.

Neosynephrin Hydrochloride N.N.R.,



differs from epinephrine hydrochloride only by the absence of the hydroxyl group in para position. While it is not nearly as active physiologically, the manufacturers claim that it is much more stable, even in alkaline solution. Synephrin tartrate, the salt of a base differing from neosynephrin only in having the hydroxyl in para position, has been dropped.

Cobresin Hydrochloride,



an accepted dental remedy, although the nearest to epinephrine in structure of those used, has only about one-twelfth of the activity. By comparison of formulas the student will see that cobresin is an isomer, having the methyl group on carbon instead of nitrogen.

Other compounds of this class that have been made are very numerous, and one or two of them we will meet in later chapters.

REVIEW QUESTIONS

- Where and in what form does benzyl alcohol occur?
- State three ways in which it can be made and write equations.
- Write the formulas of rose oil and of phenylpropyl alcohol. Suggest a way each might be made in the laboratory and write equations.
- From what official glycoside is saligenin obtained by hydrolysis? Write equation for production in the laboratory.
- Why does saligenin form salts with bases and why a color with ferric chloride?
- Write the formula of cinnamyl alcohol.
- What is the product of reducing it with nascent and with chromic acid? Write all equations.
- From what glycoside is coniferyl alcohol obtained? Where is this compound found? What is obtained on oxidation? Write equation.
- In what three ways can diphenylcarbinol be produced? Write equations.
- Why is the action of acetyl chloride on triphenylcarbinol anomalous?
- Why are there four compounds with the same formula as ephedrine? What is pseudoephedrine and how is it made? Write equations for the synthesis from benzene.
- Show by equations the synthesis of epinephrine. What must be done to the product before it can be substituted for the latter in medicine? Why?
- Why will epinephrine dissolve in either acids or bases? Write equations for each. What is the explanation of its instability?
- Write the formula of neosynephrin. Suggest a way to synthesize it.
- How does cobresin differ from epinephrine in structure?
- What are adrenalin, phenylaminoethanol, and propradrine?

CHAPTER XXX

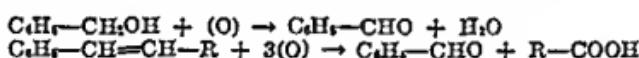
ALDEHYDES AND KETONES

ALDEHYDES

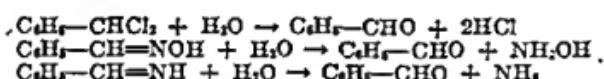
ALDEHYDES of the aromatic series may have the characteristic group connected directly to the benzene nucleus as in benzaldehyde, C_6H_5-CHO , or this radical may be attached to carbon of a side-chain. In the latter case the nucleus has smaller influence on the chemical properties, which are in general those of aliphatic aldehydes. In benzaldehyde and its substitution products, however, these properties are modified somewhat by proximity of the ring.

The aromatic compounds are designated as derivatives of benzaldehyde, such as o-nitrobenzaldehyde, $NO_2-C_6H_4-CHO$ 1:2. In complicated substances and in other cases where it is necessary to look upon the aldehyde radical as a substituent, it is called "carbonal;" $NH_2-C_6H_4-CHO$ 1:4 could be called 4-carbonalaminobenzene or p-aminobenzaldehyde.

The usual general methods for preparing aldehydes may be used equally well here, whether we deal with derivatives of benzaldehyde or with compounds that have the typical group farther removed from the benzene ring. These processes may be summarized for review as: oxidation of primary alcohols or unsaturated compounds;



hydrolysis of α,α -dihalides, oximes, imines, etc.;



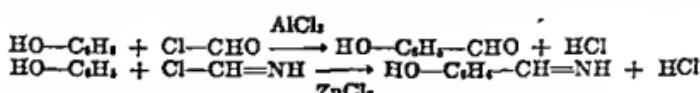
heating of salts with formates;



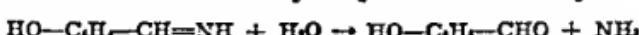
and reduction of acid derivatives by nascent hydrogen.



They may also be produced by Friedel-Crafts reaction using hydrogen cyanide or carbon monoxide with hydrogen chloride, equivalent to $Cl-CH=NH$ and $Cl-CH=O$ respectively.



Of course, the imine can then be hydrolyzed to the aldehyde.



Reactions.—In most respects they behave like aliphatic aldehydes. They add hydrogen cyanide, sodium bisulfite, and the Grignard reagent

and produce a color with Schiff's fuchsin-sulfurous acid. They are very easily oxidized by silver nitrate and even by air slowly. They form oximes, hydrazones, and semicarbazones and are converted to dihalides by phosphorus pentachloride.

In some reactions, however, the true aromatic aldehydes are markedly different, especially in their behavior to oxidation. Unlike those of the paraffin series, they do not reduce Fehling's solution. As a matter of fact, benzaldehyde and its derivatives are not nearly so easily oxidized, as demonstrated by an effect with silver nitrate but not by Fehling's solution.

The explanation for the slow but easy and complete effect by a very mild agent like air lies in the phenomenon of auto-oxidation, which is frequently encountered in the laboratory and in industry. The aldehyde absorbs a molecule of oxygen to furnish a peroxide that can be isolated.

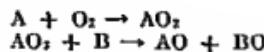


Such a compound is comparable to silver nitrate as an oxidizing agent and acts on a second molecule of aldehyde.



It could also affect any other easily oxidizable substance that might be present. Thus, if a solution of starch and potassium iodide is exposed to sunlight, the iodine is not set free to form a blue color for considerable time. But, if a layer of liquid benzaldehyde is superimposed on such a solution, the blue color appears within a very few minutes.

This phenomenon of auto-oxidation is of frequent occurrence and can be demonstrated in other ways. The most familiar example is in the "drying" of ordinary paint, where turpentine acts as the oxygen carrier to linseed oil, it itself also being changed to resins by oxygen residue. All of the terpenes, and probably all unsaturated compounds, are good auto-oxidation agents, as can be proved by the fact that metals, thoroughly covered by such substances in an atmosphere of dry air, quickly get a layer of oxide. In only one or two cases has the peroxide been isolated as with benzaldehyde, but the formation of such a compound in every instance of auto-oxidation is probable. The agent A absorbs oxygen to give such a substance and then passes half of it on to the receptive compound B or to another portion of A.



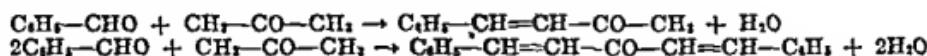
Also in other respects the aromatic aldehydes are distinguished from their relatives of the chain series. When treated with alkalies, they do not polymerize and resinify but oxidize themselves in the so-called Cannizzaro reaction, which we noted previously under formaldehyde in Chapter IX.



However, under the influence of potassium cyanide, they do undergo a bimolecular polymerization through the aldehyde groups to produce benzoin or its derivatives.



With hydrogen adjacent to an activating group like carbonyl, they react by condensation to form benzylidenes. Thus, benzaldehyde with acetone gives benzalacetone and dibenzalacetone.



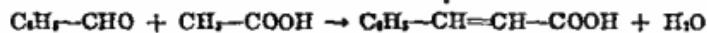
The student will recall that aliphatic aldehydes possess this property, but the aromatic compounds are much more active.

Benzaldehyde N.F., $\text{C}_6\text{H}_5\text{CHO}$, is found naturally combined with sugar and hydrogen cyanide in glycosides, especially of the Rosaceae. The bitter almond contains amygdalin that furnishes on hydrolysis Oil of Bitter Almond U.S.P., chiefly benzaldehyde with about 2 per cent of hydrogen cyanide. Wild Cherry U.S.P. contains prunasin that is very similar. It is also found as a secondary ingredient of many volatile oils and the chief component of a few like that of bitter almond mentioned above.

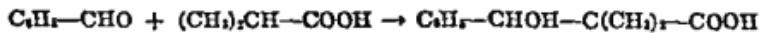
Commercially benzaldehyde is made from toluene by catalytic oxidation, using manganese dioxide and sulfuric acid in the presence of copper sulfate at 180° or chromyl chloride in carbon disulfide. Other methods first chlorinate the toluene to benzyl or benzal chloride; the former can be converted to benzyl alcohol and oxidized, and the latter hydrolyzes directly to the aldehyde, usually with lime.

Benzaldehyde is a liquid with characteristic odor, boiling at about 180° , with a specific gravity of 1.05, and easily volatile with steam. Although the pure substance is said to be more stable, the marketed article rapidly crystallizes in air to form benzoic acid. Intermediate, however, is formed benzoyl peroxide or perbenzoic acid by addition of oxygen, especially in the sunlight. The whole process may be partially prevented by the addition of antioxidants like hydroquinone.

Among the useful reactions are condensations with substances containing active hydrogen.¹ As has already been mentioned, acetone in the presence of sodium hydroxide gives benzalacetone melting at 42° and dibenzalacetone melting at 112° . Dimethylaniline or phenol in the presence of zinc chloride gives useful dyes that will be described later. The most interesting of such reactions, however, is the Perkin process, in which unsaturated acids are prepared from those of the acetic acid series. For example, with acetic anhydride and sodium acetate, benzaldehyde condenses to give cinnamic acid.



In this reaction addition probably first takes place similar to formation of aldol; indeed, if the saturated acid that is used has only one hydrogen in alpha position, the final product is such an aldol or its lactone.



The oxime of benzaldehyde exists in two modifications because of rigidity of the double bond between carbon and nitrogen. Theoretically oximes of the aldehydes and ketones of the aliphatic series should show the same sets of isomers, but only one has ever been separated. In the compounds from aromatic aldehydes and ketones, however, the phenomenon is fairly common. The two forms for benzaldehyde are designated as

syn and anti, represented by the formulas $C_6H_5-C(H)-C_6H_5$ and $C_6H_5-C(H)-C_6H_5$

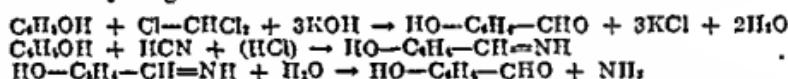


respectively.

Benzoin, $C_6H_5-\text{CHOH}-\text{CO}-C_6H_5$, colorless crystals melting to a yellow liquid at 135° , is prepared by heating benzaldehyde with potassium cyanide. It reduces silver nitrate or Fehling's solution and thereby is converted to benzil, $C_6H_5-\text{CO}-\text{CO}-C_6H_5$. The latter by fusion with caustic alkali rearranges to benzilic acid, $(C_6H_5)_2-\text{COH}-\text{COOH}$. Either benzaldehyde or benzoin will reduce with sodium amalgam to hydrobenzoin, $C_6H_5-\text{CHOH}-\text{CHOH}-C_6H_5$, or with zinc and acid to desoxybenzoin, $C_6H_5-\text{CH}_2-\text{CO}-C_6H_5$.

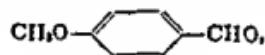
p-Dimethylaminobenzaldehyde, $(\text{CH}_3)_2\text{N}-C_6H_4-\text{CHO}$ 1:4, is an official reagent for testing urine or blood for the presence of urobilogen.

Salicylaldehyde or o-hydroxybenzaldehyde, $\text{HO}-C_6H_4-\text{CHO}$ 1:2, occurs in a number of volatile oils and as an oxidation product of the alcohol or of salicin. It can be produced from phenol with potassium hydroxide and chloroform (Reimer-Tiemann reaction) or with hydrogen cyanide and hydrogen chloride.

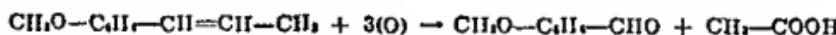


In both cases, of course, some of the para compound is also formed. The aldehyde is a liquid with a pleasant odor that boils at about 195° and gives a violet color with ferric chloride. Oxidizing agents convert it to the corresponding acid, salicylic. It reacts with acetic anhydride and sodium acetate in the Perkin reaction to yield coumarinic acid and coumarin.

Anisaldehyde or p-methoxybenzaldehyde,



occurs in the oils of anise and fennel and can be made by oxidation of anethole, their chief constituent.



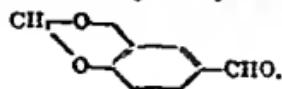
It has a pleasant odor and is used in perfumery.

Vanillin U.S.P., 3-methoxy-4-hydroxybenzaldehyde or



is contained in a number of volatile oils and particularly in Vanilla N.F. It is chiefly made synthetically today by oxidizing isoeugenol from clove oil or, increasingly important, coniferyl alcohol from sulfite waste in the manufacture of paper. Vanillin is only sparingly soluble in water but, because of its phenol group, dissolves readily in alkalies. With ferric chloride it produces a blue color, changing to brown on boiling and depositing a white precipitate of dehydrovanillin.

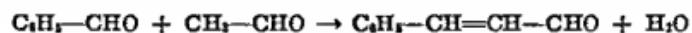
Piperonal or heliotropin, 3,4-methylenoxybenzaldehyde,



is useful as a perfuming agent. It is made by oxidizing safrole, isosafrole, or piperic acid from pepper.

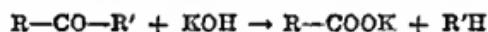
Phenylacetaldehyde, $C_6H_5-CH_2-CHO$, has an odor similar to rose and is also used in perfumery.

Cinnamaldehyde N.F., or 3-phenylpropenal, $C_6H_5-CH=CH-CHO$, is the chief ingredient of Oil of Cinnamon U.S.P. and other preparations of cinnamon. It can be prepared in the laboratory by condensing benzaldehyde with acetaldehyde in the presence of dilute alkali.

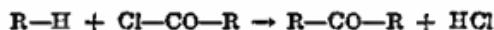


KETONES

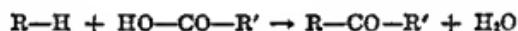
Aromatic ketones have reactions similar to those of the aliphatic series, practically the same if the carbonyl is far enough from the ring. Those in which this is attached directly are in general more easily altered by oxidation, reduction, or high temperature. Reduction by zinc amalgam and acid (Clemmensen) proceeds readily to the hydrocarbon, whereas aliphatic ketones go only to the secondary alcohol. Fusion with potassium hydroxide results in cleavage to a hydrocarbon and a salt.



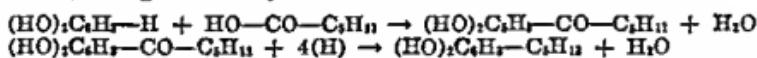
The aromatic ketones are prepared by the methods described in Chapter X and also by the Friedel-Crafts reaction using acyl chlorides.



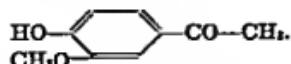
With polyphenols this process may be brought about using acids of the acetic series.



With resorcinol and caproic acid and subsequent reduction by Clemmensen's method, one gets n-hexylresorcinol.

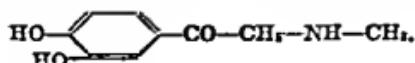


Acetophenone, $C_6H_5-CO-CH_3$, which occurs in several oils, has been used in medicine under the title of "Hypnone." It is made synthetically by passing the vapors of benzoic and acetic acids over manganese dioxide at about 600° , by heating a mixture of the salts of these two acids, or from benzene by action of acetyl chloride or acetic anhydride. Acetophenone gives the haloform reaction and in other respects behaves like acetone, although it will not add sodium bisulfite. Several derivatives occur in nature, among them p-hydroxyacetophenone which is obtained from glycosides in several plants. Apocynin, obtained from apocynum, is 4-hydroxy-3-methoxyacetophenone,



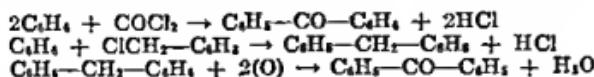
Halogen substitution products of acetophenone are used as lachrymators, and p-aminoacetophenone and its diazotized solution are official reagents.

Kephrene Hydrochloride N.N.R.,



the last step in the synthesis of epinephrine is used like the latter in medicine.

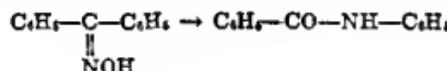
Benzophenone, $C_6H_5-CO-C_6H_5$, a solid melting at about 48° , contains no alpha hydrogen, so it does not enter into condensations like acetone, nor does it add sodium bisulfite. In other respects it behaves like ketones in general. By Clemmensen's reduction it is converted to dipbenylmethane. Benzophenone is made commercially from benzene and phosgene or benzyl chloride in the presence of aluminum chloride.



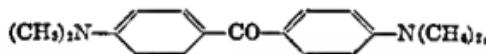
Carbon tetrachloride or benzoyl chloride can also be used in place of the phosgene. Another method is to heat calcium benzoate or benzoic acid in the presence of manganese dioxide.



The oximes of benzophenone and others of its class, when treated with acetyl chloride or phosphorus pentachloride, undergo what is known as the Beckmann rearrangement. The hydroxyl group of the oxime and the aromatic radical that is anti to it change places to produce the enol of an amide. Thus, benzophenone oxime rearranges to benzanilide.

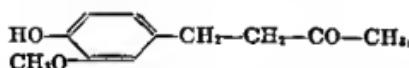


Michler's ketone,



made by the action of phosgene on dimethylaniline, is used in making dyes.

Zingerone, 4-hydroxy-3-methoxybenzylacetone,



is one of the constituents of ginger oil. It may be synthesized by the action of vanillin and acetone with subsequent reduction.

Among others of this class may be mentioned: anisic ketone, $CH_3OC_6H_4-COCH_3$; benzalacetone, $C_6H_5CH=CH-CO-CH_3$, which has already been noted, and its reduction product, benzylacetone; dibenzalacetone and dibenzylacetone; benzoin and benzil, which were noted as products from benzaldehyde.

QUINONES

Oxidation of aniline, phenol, hydroquinone, and other substitution products of benzene yields a substance known as quinone, $C_6H_4O_2$. This can be very easily reduced by sulfur dioxide or nascent hydrogen to hydroquinone, $C_6H_6O_2$. Since it reacts with hydroxylamine to form a monoxime and a dioxime, it can be assumed that quinone is twice a ketone. Unlike

benzene, it adds in 4 atoms of bromine and must contain two double bonds. Therefore, we conclude that it is a diketocyclo-olefine with the formula,

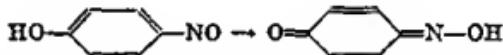
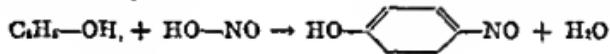


The remarkable change from quinol,



to this quinone and vice versa, with the necessary alteration in resonance of the benzene nucleus, is but one illustration of several such conversions. We have already noted one in the ketone-enol isomerism of phloroglucinol.

Quinone is a yellow, crystalline substance with a characteristic pungent odor and melting at 116° . It is volatile with steam, making it possible to separate it from non-volatile impurities. Its monoxime may be produced by the action of nitrous acid on phenol, necessitating another such change to an alicyclic nucleus.



With equimolecular quantities of quinol evaporated from ether solution, there is obtained beautiful, greenish crystals of quinhydrone, $\text{C}_6\text{H}_4\text{O}_2 \cdot \text{C}_6\text{H}_6\text{O}_2$. This dissolves in ether again to a colorless solution, showing complete dissociation into the components.

Other phenols also oxidize to quinones with the structure of 1,4-diketones. Toluquinone from the cresols, thymoquinone from thymol, and xyloquinone from the xlenols are illustrations. Each can be reduced to the corresponding hydroquinones and reproduced again by oxidation. Each forms with any hydroquinone a molecular quinhydrone, which is in all cases beautifully crystalline but colorless in ether solution. It is probable that the autumn foliage of deciduous trees owes at least part of its colors to the formation of quinhydrone.

Orthoquinones are also known, but are of much less importance. Catechol, for example, can be oxidized by silver oxide to o-benzoquinone,



REVIEW QUESTIONS

- State five different methods for the preparation of aromatic aldehydes and write equations.
- In what respects do they behave like the aliphatic aldehydes?
- Explain auto-oxidation and illustrate with equations.
- Write an equation to show the Cannizzaro reaction. How would aliphatic aldehydes behave under the same conditions?
- In what official drugs does benzaldehyde occur? State two ways in which it is obtained from toluene and write equations for each.
- Illustrate the Perkin reaction by an equation. With what other substances will aromatic aldehydes condense in the same way?

7. Illustrate the syn and anti forms of benzaldehyde oxime.
8. Write the formulas of salicylic aldehyde and of vanillin. Why do they dissolve in alkalies?
9. How is cinnamic aldehyde prepared in the laboratory? Of what oil is it the chief ingredient?
10. Write equations to show oxidation of anethole to anisaldehyde and of safrole to piperonal.
11. In what anomalous way do ketones behave in reducing with zinc amalgam (Clemmensen)?
12. What happens when the ketone is heated with caustic alkali? Write equation.
13. Show by an equation production of a ketone by the Friedel-Crafts reaction.
14. Write the formulas of acetophenone, benzophenone, and kephrine hydrochloride.
15. How is quinone made? What is formed on reduction? Write equations.
16. What is a quinhydron? an orthoquinone? Illustrate each.

CHAPTER XXXI

AROMATIC ACIDS

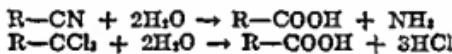
WHAT has been said about influence of the nucleus on properties of alcohols, aldehydes, and ketones applies equally well to the acids. When the carboxyl group is attached to carbon of a side-chain, this influence is very small and the compound is much like members of the acetic series. When it is connected to the ring, that is in benzoic acid and its derivatives, some modification may be expected. The monobasic-acids we have met so far show little tendency to lose carbon dioxide, but this is greatly increased in the substitution products of benzoic acid. The compounds are mostly insoluble in cold water, but soluble hot, and are generally stronger acids because of negative character of the benzene ring.

Preparation.—Most of the methods are those that we have already learned and need no additional discussion here, but a few are typical of the aromatic series only.

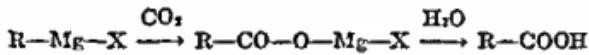
1. The corresponding primary alcohol can be oxidized to aldehyde and the latter again to the acid, either directly with agents or indirectly through the Cannizzaro reaction.



2. The cyanide or amide can be converted by boiling with dilute acids or bases. Compounds containing 3 halogen atoms connected to 1 carbon, as in benzotrichloride, hydrolyze similarly.



3. The Grignard reagent, made with an aryl halide, may be added to carbon dioxide and then hydrolyzed.



4. The sulfonic acids can be converted to nitriles by fusing the salts with potassium cyanide.



5. The nitro compounds or amines can be changed to nitriles through the Sandmeyer diazo reaction.



6. As discussed in detail previously, any side-chain can be oxidized to a carboxyl, but in this case the ease with which other substituents react to oxidizing agents must be considered. Any alkylbenzene gives benzoic acid, dialkylbenzenes give dibasic acids, and each side-chain produces a carboxyl group. Of the twelve possible mono and poly products of benzene, all but two, C_6H_5-COOH and one $C_6H_2(COOH)_2$, have been obtained from coal by oxidation, giving us a partial picture of the structure of carbon in coal.

Benzoic Acid U.S.P., C_6H_5-COOH , occurs in the free state and as esters in many resins, oils, fruits, and other plant products. In the urine it is found combined with amino-acetic acid as hippuric acid, $C_6H_5-CO-NH-CH_2-COOH$. It is manufactured in commerce by hydrolysis of benzotrichloride with lime or water in the presence of iron at 50° , by heating phthalic acid with zinc oxide, or by the catalytic oxidation of toluene or benzyl chloride.

Benzoic acid melts at 122° and boils at 249° , but can easily be sublimed, is volatile with steam, and has a faint, pungent odor. The solubility is about 0.25 per cent at 15° , but it dissolves readily in hot water. The dissociation constant is 6.6×10^{-5} , compared with acetic acid 1.8×10^{-5} .

Sodium Benzoate U.S.P., much employed as preservative, has been found not dangerous in foods in spite of the intense controversy that was waged a few decades ago. Lithium Benzoate N.F., Mercuric Benzoate N.N.R., and ammonium benzoate are also sometimes used.

Benzoyl chloride, $C_6H_5-CO-Cl$, is produced by the action of phosphorus pentachloride on benzoic acid, but in commerce it is made by the action of chlorine on benzaldehyde.



It is an insoluble liquid with an intense, pungent odor. The compound is chiefly of value as a benzoylating agent for converting alcohols and amines to esters and amides of benzoic acid. In the Schotten-Baumann reaction for this purpose, the chloride is gradually added to an alkaline solution of the alcohol or amine. Benzamide, $C_6H_5-CO-NH_2$, melting at 130° , is produced with ammonia, while aniline gives benzanilide, $C_6H_5-CO-NH-C_6H_5$, melting at 163° . The p-nitrobenzoyl chloride is also often employed to make crystalline compounds for identification.

Benzonitrile, C_6H_5-CN , a liquid with an odor similar to nitrobenzene, is produced through the diazo reaction from aniline, by dehydrating benzamide, or from the sulfonic acid by fusion with potassium cyanide.

Benzoyl peroxide (Novadrol), $C_6H_5-CO-O_2-CO-C_6H_5$, is prepared by treating benzoyl chloride with sodium peroxide. It is rather more stable than other organic peroxides and is occasionally used in the treatment of burns and of dermatitis from poison ivy. Acetone or benzoyl-acetyl peroxide was formerly employed in medicine but is rather dangerous.

Benzoic anhydride is formed by heating benzoyl chloride with sodium benzoate at 130° . It is a colorless, crystalline powder that is insoluble in water and only slowly converted by it to the acid.

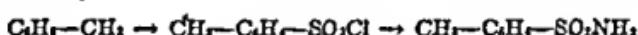
Hippuric acid (benzoylglycine), $C_6H_5-CO-NH-CH_2-COOH$, is found in the urine, particularly of horses. Hippuran, N.N.R., sodium o-iodohippurate, is recommended in medicine for its content of iodine.

Ethyl benzoate has a characteristic odor that may be used to identify ethyl alcohol, benzoic acid, and many compounds which furnish these on hydrolysis. Thus, it is formed from cocaine by heating with sulfuric acid. Benzyl benzoate, $C_6H_5-CH_2-O-CO-C_6H_5$, was formerly much used in medicine for its action in relaxing muscles. It is an insoluble liquid and was most popular in the form of an emulsion.

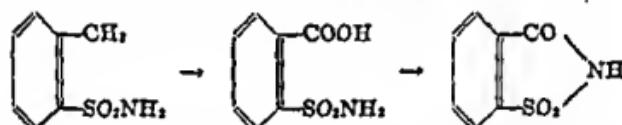
Several local anesthetics are simple esters of benzoic acid and of the general type of procaine. Alypin Hydrochloride N.N.R., used largely in

urology, is the salt of 1-dimethylamino-2-henoxy-2-dimethylaminomethylbutane, $\text{C}_6\text{H}_5-\text{CO}-\text{O}-\text{C}(\text{CH}_2-\text{CH}_3)-\text{CH}_2-\text{N}(\text{CH}_3)_2$. Stovaine, formerly much used in a similar way, is 1-dimethylamino-2-methyl-2-henoxybutane, $\text{C}_6\text{H}_5-\text{CO}-\text{O}-\text{C}(\text{CH}_2-\text{CH}_3)-\text{CH}_2-\text{N}(\text{CH}_3)_2$. Metycaine, a more recent compound, is a derivative of piperidine and will be considered later.

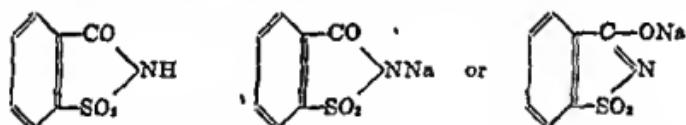
Saccharin U.S.P. (Gluside, Benzosulfonide) is the imide of o-sulfohenzoic acid, $\text{HOOC}-\text{C}_6\text{H}_4-\text{SO}_2-\text{OH}$ 1:2. It is many times sweeter than sucrose and, although it has no nutritive value, is employed as flavoring agent in the diet of the diabetic patient. In the manufacture of saccharin, toluene is first converted to o-toluenesulfonchloride by heating with chlorosulfonic acid, and this is then transformed to the corresponding amide by addition of ammonia.



When this is oxidized by potassium permanganate, the methyl group becomes carboxyl and dehydration gives saccharin.



The product is not very soluble in water but dissolves easily in ammonia water or solutions of alkalies, whereby the imide hydrogen is displaced by metal; in reality there is rearrangement to the enol formula.



Saccharin Sodium U.S.P., the latter with two molecules of water, is the form in which it is usually administered.

Halazone N.N.R., p-sulfonedichloramidobenzoic acid or $\text{HOOC}-\text{C}_6\text{H}_4-\text{SO}_2-\text{NCl}_2$ 1:4, is used as antiseptic and disinfectant like chloramine and dichloramine.

Anthranilic acid or o-aminobenzoic acid, $\text{NH}_2-\text{C}_6\text{H}_4-\text{COOH}$ 1:2, consists of colorless crystals that are soluble in acid in either case. It is made by nitrating toluene, and then reducing to the amino derivative. In the synthesis of indigo and in the preparation of dyes, it has pleasant odors and is used to substitute the odor of grapes, and is found in the oils of citrus fruits. It is also used in the manufacture of dyes.

as to form salt to o-nitrobenzoic acid is unique. Its ester is a derivative of benzoic acid.

ami

Several local anesthetics of the i benzoic acid, an official reagent. The benzoate U.S.P. (Benzocaine, Anesthetic) 1:4. Ethyl Aminobenzoate U.S.P. (

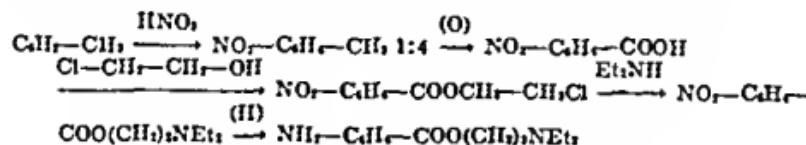
ester, is employed as such and in the form of Batesin Picrate N.N.R., which is popular for the treatment of burns. Propaesine, the propyl ester, and Cycloform, the isobutyl compound, are others.

Many soluble local anesthetics to be used by injection or infiltration like cocaine are also derivatives of p-aminobenzoic acid. The theory surrounding their original preparation was based on certain groupings in cocaine. In the generalized simple formula for these, $R_2N-(CH_2)_xOOC-C_6H_5$, the various anesthetics can be derived by altering the amino radicals, by changing the value of x , by substituting for hydrogen in the methylene groups, or finally making substitution for hydrogen in the ring. Representatives of each possible kind have been made, and all of them have been found to be local anesthetics. The particular compounds that we are considering here all have an NH_2 group para to the carboxyl residue.

Considering here all have an NH_2 group plus to the following:

Procaine Hydrochloride U.S.P. (Novocaine), $(\text{CH}_3-\text{CH}_2)_2\text{N}-\text{CH}_2-\text{CH}_2-\text{OOC-C}_6\text{H}_4-\text{NH}_2 \cdot \text{HCl}$ 1:4, is the most popular of all local anesthetics that are synthetic. It is soluble in water or alcohol and is precipitated from its aqueous solution by alkalies or alkali carbonates, although it is compatible with bicarbonates. The free base that is so precipitated is anesthetic and sometimes used, also its borate and nitrate, described in N.N.R. **Butacaine Sulfate U.S.P.** (Butyn) is di-n-butylaminopropyl-p-aminobenzoate sulfate, $\text{Bu}_2\text{N}(\text{CH}_2)_2\text{OOC-C}_6\text{H}_4-\text{NH}_2 \cdot \text{H}_2\text{SO}_4$. **Tutocaine Hydrochloride N.N.R.** is 2-p-aminobenzoxy-3-methyl-4-dimethylaminobutane hydrochloride, $(\text{CH}_3)_2\text{N}-\text{CH}_2-\text{CH}(\text{CH}_3)-\text{CH}(\text{CH}_3)-\text{OOC-C}_6\text{H}_4-\text{NH}_2 \cdot \text{HCl}$. **Larocaine Hydrochloride N.N.R.** is 1-p-aminobenzoxy-2,2-dimethyl-3-diethylaminopropane hydrochloride, $\text{Et}_2\text{N}-\text{CH}_2-\text{C}(\text{CH}_3)_2-\text{CH}_2-\text{OOC-C}_6\text{H}_4-\text{NH}_2 \cdot \text{HCl}$. **Tetracaine Hydrochloride U.S.P.** (Pontocaine Hydrochloride) is dimethylaminoethyl p-butylaminobenzoate hydrochloride, $(\text{CH}_3)_2\text{N}-\text{CH}_2-\text{CH}_2-\text{OOC-C}_6\text{H}_4-\text{NH}-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{C}_6\text{H}_4-\text{NH}_2 \cdot \text{HCl}$. Still another of this class is **Amylcaine Hydrochloride N.N.R.**, 2-amylaminoethyl p-aminobenzoate hydrochloride, $\text{NH}_2-\text{C}_6\text{H}_4\text{COO-C}_6\text{H}_4-\text{CH}_2-\text{NHAm} \cdot \text{HCl}$.

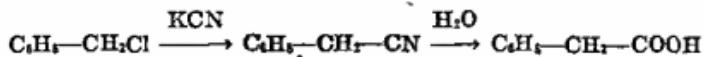
The manufacture of any of these compounds is illustrated by the method used for procaine. This is indicated in outline without discussion, because the reactions involved are well known to the student.



Many of the alkyl derivatives of benzoic acid are known, but in only a few cases are they important enough to warrant discussion here. The three toluiic acids, $\text{C}_6\text{H}_5\text{CH}_2\text{COOH}$, prepared by partial oxidation of the xylenes, are sparingly soluble solids like benzoic acid. Cuminic acid, p-isopropylbenzoic acid, $(\text{CH}_3)_2\text{CH-C}_6\text{H}_4\text{COOH}$ 1:4, is prepared by the oxidation of cymene and some other natural materials. 2,6-Dialkylbenzoic acids are excellent examples of steric hindrance, since they cannot be esterified readily in the usual way. The esters once formed, however, are very resistant to hydrolysis.

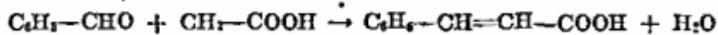
Phenylacetic acid, $C_6H_5-CH_2-COOH$, is a sparingly soluble solid that

is weaker than benzoic but stronger than acetic acid. It can be prepared from benzyl chloride through the cyanide.

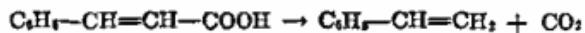


Its esters are commonly found in volatile oils and are used in perfumery. Phenylpropionic acid (hydrocinnamic acid), $\text{C}_6\text{H}_5\text{—CH}_2\text{—CH}_2\text{—COOH}$, is similar.

Cinnamic acid, $\text{C}_6\text{H}_5\text{—CH=CH—COOH}$, occurs commonly in oils, gums, and halsams, usually in the form of esters with benzyl or cinnamyl alcohol. It is a solid that has a sharp, persistent odor, is slightly soluble in cold water, and melts at 133° . It can be made synthetically by the Perkin reaction from benzaldehyde and acetic anhydride.



When it is heated with sodium hydroxide, it loses carbon dioxide and becomes converted to styrene.



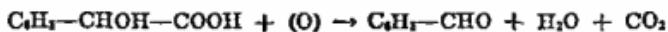
Because cinnamic acid contains the double bond, it must have a geometric isomer. Allocinnamic acid, which is believed to be the cis form, sometimes occurs in nature and is known in at least three crystallographic modifications.

Apothesine Hydrochloride N.N.R. is one of the local anesthetics of the procaine class, but is derived from cinnamic acid instead of benzoic acid. It is diethylaminopropyl cinnamate hydrochloride, $\text{Et}_2\text{N—CH}_2\text{—CH}_2\text{—CH}_2\text{—OOC—CH=CH—C}_6\text{H}_5\cdot\text{HCl}$.

Mandelic Acid U.S.P., $\text{C}_6\text{H}_5\text{—CHOH—COOH}$, contains an asymmetric carbon atom but is described as the racemic form. The influence of the hydroxy group is reflected in the solubility, for it is fairly soluble in water. It can be made from benzaldehyde by addition of hydrogen cyanide and subsequent hydrolysis.



The levo form can be prepared by careful hydrolysis of amygdalin, but ordinarily this gives benzaldehyde, hydrogen cyanide, and d-glucose. Mandelic acid melts at about the same temperature as benzoic acid but can easily be distinguished by its solubility, its reactions as hydroxy acid, and by its oxidation to benzaldehyde.

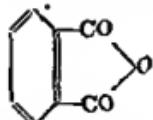


The acid is used to make homatropine and several other drugs. Calcium Mandelate U.S.P. and preparations of the ammonium salt are used in medicine.

Tropic acid, $\text{C}_6\text{H}_5\text{—CH(CH}_2\text{OH)—COOH}$, a homologue of mandelic acid, is a hydrolytic product of atropine. Upon dehydration it is converted to atropic acid, $\text{C}_6\text{H}_5\text{—CH(=CH}_2\text{)—COOH}$.

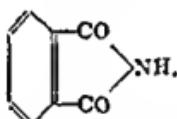
Syntropan N.N.R., 1-tropoxy-2,2-dimethyl-3-diethylaminopropane phosphate, $\text{C}_6\text{H}_5\text{—CH(CH}_2\text{OH)—COO—CH}_2\text{—C(CH}_3)_2\text{—CH}_2\text{—N(CH}_2\text{—CH}_3)_2\text{—}\frac{1}{3}\text{H}_3\text{PO}_4$, is used in place of atropine. A compound used similarly is Trasentin, $(\text{C}_6\text{H}_5)_2\text{CH—COO—CH}_2\text{—CH}_2\text{—NET}_3\text{·HCl}$.

Phthalic acid, o-benzeneddicarboxylic acid, $C_6H_4(COOH)_2$, 1:2, is obtained from naphthalene or o-xylene by oxidation. The product that is obtained in such a process, and the form in which it is used commercially, is the anhydride,

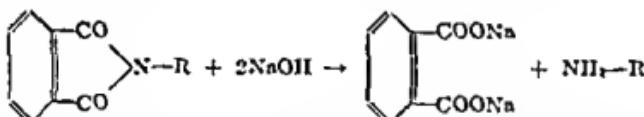


The acid itself can be prepared by dissolving this in alkalies and reprecipitating by addition of mineral acids. When it is heated to just above its melting point, there is a loss of water and conversion to the anhydride. The latter is a colorless solid that can be sublimed to beautiful, very stable crystals. When it is heated with ammonia, an imide is formed in exactly the same way as is that from succinic anhydride. Many million pounds of the anhydride are produced annually, most of it to be used in the manufacture of glycerophthalic (glyptal) resins, very important industrial substances, some in the production of anthraquinone and phthalein dyes. Some of the esters of phthalic acid are also important as solvents and plasticizers and in the manufacture of lacquers. Potassium acid phthalate is an official reagent.

Phthalimide,



is useful in the Gabriel process for making primary amines free from secondary and tertiary compounds. The hydrogen can be displaced by metals, and the resulting salts will react with alkyl halides to furnish alkyl substitution products of phthalimide. When such a compound is hydrolyzed by warming with dilute bases, the primary amine is set free and can be distilled.



Isophthalic acid, the meta compound, and terephthalic acid, the para derivative, $C_6H_4(COOH)_2$, are colorless, insoluble, crystalline solids that can be prepared by oxidation of the corresponding xylenes.

Mellitic acid, $C_6(COOH)_4$, is interesting in that it can be formed by the oxidation of coal or graphite. The aluminum salt, $Al_2C_{12}O_{12} \cdot 18H_2O$, is found in seams of coal and, from its appearance, is called "honey stone."

REVIEW QUESTIONS

- How do aromatic acids compare with those of the acidic series in solubility, dissociation, and tendency to lose CO_2 ?
- State six methods for producing them and write an equation to illustrate each.
- Show how benzoic acid is obtained from toluene, benzotrichloride, and phthalic acid.
- Name three metallic benzoates that are used in medicine.
- What is the Schotten-Baumann process and for what is it used? Write an equation to illustrate.

6. Write formulas of benzonitrile, benzoic anhydride, benzoyl peroxide, hippuric acid, bippuran, ethyl benzoate, and alypin hydrochloride.
7. Outline the method for manufacturing saccharin and write equations. What is soluble saccharin?
8. Write equations for the preparation of anthranilic acid. Where does it occur in nature?
9. Give formulas of benzocaine and butesin. What is the general formula for anesthetics of this class?
10. What is the general formula for anesthetics of the procaine class? How is this varied in the compounds used? Write formulas of procaine and name four others of the class.
11. Outline the method of synthesizing procaine.
12. Write formulas of o-toluic acid, cuminic acid, phenylacetic acid, phenylpropionic acid.
13. How is cinnamic acid made? Write equation. What is the relation of allocinnamic acid?
14. Which form of mandelic acid is official? Write equation for oxidizing it to benzaldehyde.
15. Write equations for production of phthalic acid, its anhydride, and its imide. Which of these is important in commerce and for what purpose?
16. What is the Gabriel process for preparing primary amines? Write an equation to illustrate.

CHAPTER XXXII

PHENOLIC ACIDS

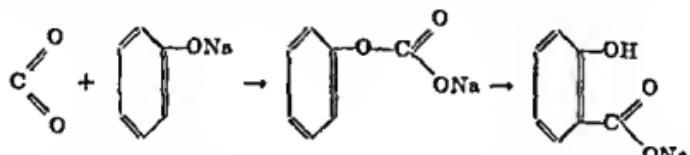
THE chief reasons for setting apart the phenolic acids are the importance of the many compounds represented and the minor differences in reactions. The properties encountered are those of phenols and those of acids, but there is the additional influence of the hydroxyl group to make them stronger acids and to increase the tendency to lose carbon dioxide. The compounds belonging to the class are crystalline and in general more soluble and less volatile than the corresponding phenols. Both hydroxyl and carboxyl groups can form salts by action of alkalies, but carbonates react only with the carboxyl. Residual hydrogen of the nucleus is more easily substituted by nitro, halogen, or sulfonic radicals than in the acid, just as reaction takes place more readily with the phenol than with the hydrocarbon.

Of the varied methods for preparing, a few are listed, practically none of which requires any discussion. Starting with the phenolic group already

ceeding through the Sandmeyer cyanide reaction from a nitro or amino group; (4) chlorinating completely a methyl group and hydrolyzing; (5) fusing a sulfonic group with potassium cyanide; and (6) using the Kolbe method to be described later. If we started with the carboxyl already present, the hydroxyl could be introduced; (7) from nitro or amino by diazotization; (8) from halogen through the Grignard reagent and oxygen; and (9) from sulfonic by fusion with alkali.

Salicylic Acid U.S.P., o-hydroxybenzoic acid, HO—C₆H₄—COOH 1:2, occurs naturally in the form of esters in many plants, probably as glycosides. The most notable of these is gaultherin of wintergreen, which furnishes methyl salicylate upon hydrolysis. Birch bark and other plants contain similar glycosides.

In commerce the acid is manufactured by a modification of the Kolbe process starting with sodium phenate. This is treated with carbon dioxide under pressure at about 130°, when addition takes place to form sodium phenyl carbonate, and this rearranges to sodium salicylate.



Under the conditions employed, very little of the para compound is formed, but at higher temperatures or using the potassium salt, the substitution goes chiefly in the para position. The Kolbe synthesis has very wide applications to the preparation of other phenolic acids, even of some in which the phenol group has been alkylated. In addition to this method, salicylic acid could be made: by oxidation of saligenin, salicylic aldehyde, or salicin;

by fusing coumarin, indigo, o-cresol, or other compounds with caustic alkali; or by diazotization of anthranilic acid.

For medicinal use the claim is often made that the natural acid (true) or a salt made from it is different than that made synthetically, and some prescriptions still call for it in preference. While the natural acid is undoubtedly accompanied by small amounts of other substances if it has not been purified properly, yet it would be difficult to maintain that these have any effect on the therapeutic results.

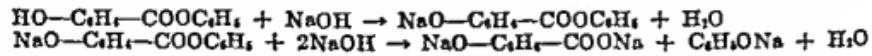
Salicylic acid consists of colorless, fluffy crystals that are very sparingly soluble in cold water, but dissolve readily in hot water, also in cold solutions of alkalies or alkali carbonates. It can be sublimed but thereby loses some carbon dioxide and is partly converted to salol. Ferric chloride gives a violet-red color with the acid or its salts.

Sodium Salicylate U.S.P., the mono salt, is formed by the action of the acid on sodium carbonate; with sodium hydroxide the phenolic hydrogen would also be displaced to give disodium salicylate. The official salt is a phenol like the acid and gives a violet-red color with ferric chloride. When an aqueous solution is acidified, as with other salts also, salicylic acid is precipitated. Ammonium Salicylate N.F., Lithium Salicylate N.F., and Strontium Salicylate N.F. are other soluble salts that are much less useful. Mercuric Salicylate U.S.P. is employed for intramuscular injection as a vehicle for mercury, while Bismuth Subsalicylate U.S.P. is applied in a similar way for administering bismuth.

The importance of salicylates in therapy has brought about the introduction of hundreds of derivatives, and many of these are popular at the present time. In order to produce these, hydrogen of the carboxyl group can be displaced by alkyl to give esters, that of the phenol group by alkyl or acyl to yield ethers and esters respectively, or hydrogen of the nucleus may also be substituted. Representatives of all of these and of combinations are among those now marketed.

Methyl Salicylate U.S.P. is the title of an article that can be made synthetically or produced by distillation of wintergreen or birch bark, but it must be labeled accordingly and have at least 98 per cent of the ester. It is only slightly soluble in water, but the aqueous solution gives a violet color with ferric chloride. Ethyl Salicylate N.N.R. is similar in physical and chemical properties and in medicinal applications. Sal-ethyl Carbonate N.N.R. is the carbonate of it.

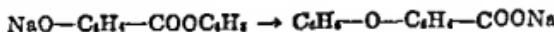
Phenyl Salicylate U.S.P. (Salol) is practically insoluble in water and gives no color with aqueous ferric chloride, although phenolic. It passes through the stomach unchanged but is dissolved by the alkalinity in the intestines, sometimes with hydrolysis to salicylates and phenol.



Because of this stability in acid solution, salol is used to give an enteric coating to pills, when these contain compounds that are designed for effects in the intestines and that might otherwise be destroyed or altered in the stomach. Salol is made by simply heating salicylic acid to about 220°; one molecule loses carbon dioxide to yield phenol and this esterifies another molecule.



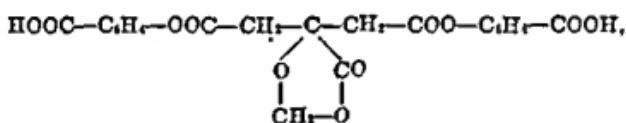
The sodium salt, when heated to about 300°, undergoes a remarkable change, in which sodium and phenyl simply exchange places to give o-phenoxybenzoic acid.



Mesotan (Salmester) N.N.R., methoxymethyl salicylate, $\text{CH}_3-\text{O}-\text{CH}_2-\text{OOC}-\text{C}_6\text{H}_4-\text{OH}$, is a liquid that behaves like the methyl ester and is used like it in medicine. Spirosal N.N.R. (Glysal), the 2-hydroxyethyl ester, $\text{HO}-\text{CH}_2-\text{CH}_2-\text{OOC}-\text{C}_6\text{H}_4-\text{OH}$, is a liquid that is almost odorless. Phenetsal N.N.R. (Salophen), acetyl-p-aminophenyl salicylate, $\text{CH}_3-\text{CO}-\text{NH}-\text{C}_6\text{H}_4-\text{OOC}-\text{C}_6\text{H}_4-\text{OH}$, is very much like salol in its physical and chemical properties.

Acetylsalicylic Acid U.S.P. (Aspirin), $\text{CH}_3-\text{CO}-\text{O}-\text{C}_6\text{H}_4-\text{COOH}$ 1:2, is probably the most used of all drugs and is undoubtedly familiar to every student. Nearly five million pounds of aspirin was produced in the United States in 1938. It is made by heating the acid with acetic anhydride and then distilling until no more comes over at 160°, the residue being recrystallized. It is perfectly stable in dry air but will slowly decompose when moist into acetic and salicylic acids, so that a test for the latter is included in the standards. Salts have been tried as soluble preparations, but the acid itself is preferable because the rate of hydrolysis becomes very rapid just as soon as a solution is made. The melting point of aspirin is variable if rigid conditions are not observed.

Novaspirin N.N.R. (Salicitrin), methylenecitrylsalicylic acid,



is made from citric and salicylic acids and formaldehyde. Salsal N.N.R. (Diplosal), salicylsalicylic acid, $\text{HO}-\text{C}_6\text{H}_4-\text{COO}-\text{C}_6\text{H}_4-\text{COOH}$, is another drug of this type. A combination of esters is represented in acetyl-salol or phenyl acetyl salicylate, $\text{CH}_3-\text{COO}-\text{C}_6\text{H}_4-\text{COOC}_6\text{H}_5$.

Mersaly U.S.P. (Salyrgan) is sodium o-[(3-hydroxymercuri-2-methoxypropyl)carbamyl]-phenoxyacetate, $\text{NaOOC}-\text{CH}_2-\text{O}-\text{C}_6\text{H}_4-\text{CO}-\text{NH}-\text{C}_6\text{H}_5(\text{OCH}_3)$ (HgOH), made by interaction of mercuric acetate, methyl alcohol, and salicylallylamido-o-acetic acid. It is used with theophylline as a diuretic.

3,5-Dinitrosalicylic acid and sulfosalicylic acid are described as official reagents.

Merthiolate N.N.R. (Merthiolate Sodium), sodium ethylmercurithiosalicylate, $\text{C}_2\text{H}_5-\text{CH}_2-\text{Hg}-\text{S}-\text{C}_6\text{H}_4-\text{COONa}$ 1:2, is used in very dilute solution as an antiseptic. It is incompatible with acids which liberate insoluble ethylmercurithiosalicylic acid. Sulfosalicylic acid is an official reagent.

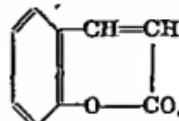
The isomeric hydroxybenzoic acids give no color with ferric chloride. The para compound can be made the chief product of the Kolbe reaction on phenol. Anisic acid, the methyl ether, $\text{CH}_3\text{O}-\text{C}_6\text{H}_4-\text{COOH}$ 1:4, is a product of oxidizing anethole and is contained with it in anise and fennel

oils. It can be made synthetically from the acid by methyl alcohol and methyl iodide in the presence of alkali.



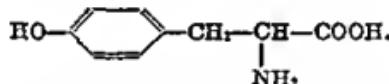
It is not a phenol and, therefore, is monohasic. Methyl Parahydroxybenzoate N.F. is used as a preservative, while Orthoform N.N.R., used like benzocaine as local anesthetic, is methyl 4-hydroxy-3-aminobenzoate, $\text{HO}-\text{C}_6\text{H}_3(\text{NH}_2)\text{COOCH}_3$, 1:2:4.

Coumaric acid or o-hydroxycinnamic acid, $\text{HO}-\text{C}_6\text{H}_4-\text{CH}=\text{CH}-\text{COOH}$ 1:2, is the trans form. The cis modification, known as coumarinic acid, readily yields an anhydride, Coumarin N.F.,

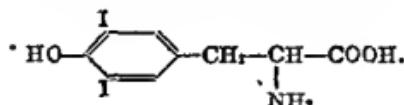


which occurs in the Tonka bean and in other plants and is used to make artificial vanilla extract. It can be synthesized by the Perkin process from salicylic aldehyde. Hydrocoumaric acid, $\text{HO}-\text{C}_6\text{H}_4-\text{CH}_2-\text{CH}_2-\text{COOH}$ 1:2, is found in nature as melilotic acid.

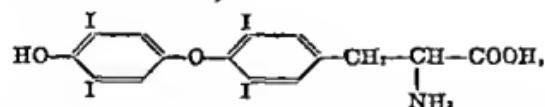
Tyrosine, an important amino acid from protein metabolism, is levorotatory 3-p-hydroxyphenyl-2-aminopropanoic acid,



It loses carbon dioxide when heated and becomes converted to tyramine. Diiodotyrosine or iodothyroic acid, an amino acid from the thyroid gland, is

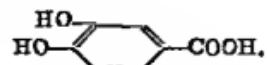


Thyroxin U.S.P. (Thyroxine),



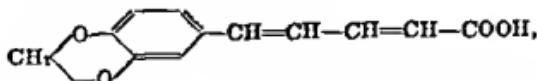
presumably one of the potent materials or hormones from the thyroid gland, is used like the latter in medicine. It is now made synthetically. Thyroxine is insoluble in water or alcohol but dissolves in alkalies or in hot solutions of carbonates.

Protocatechuic (catechuic) acid,-

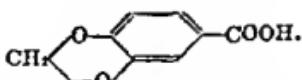


is prepared by fusing with potassium hydroxide various resins, such as kino, benzoin, or catechu from which the name is derived. By heating it can be converted to pyrocatechin or catechol. With ferric chloride it

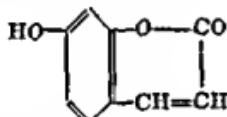
gives a green color. The dimethyl ether is known as veratric acid, occurring in veratrum species, and the monomethyl ether in position 3 is vanillic acid, corresponding to vanillin and easily made from it by oxidation. Other natural acids derived from it are: caffeoic acid, 3,4-dihydroxycinnamic acid, named from coffee; and piperic acid,



combined with piperidine in pepper. Oxidation of the former gives catechuic acid, of the latter piperonal and piperonylic acid,

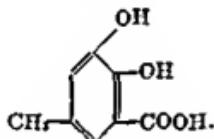


Umhelliferone, the anhydride of 2,4-dihydroxycinnamic acid,

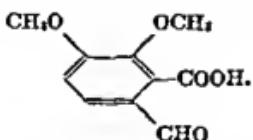


is used in industry as a light screen. Its methyl ether is found in volatile oils.

Orsellinic acid, occurring in lichens, is a dihydroxy derivative of m-toluic acid having the formula,



Opianic acid, found in opium and also a product of oxidizing narcotine or hydrastine, is 2,3-dimethoxy-6-carbonalbenzoic acid,

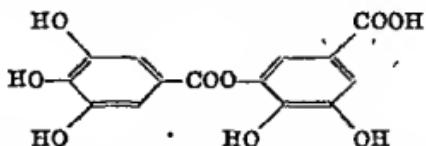


Gallic Acid N.F., $(\text{HO})_3\text{C}_6\text{H}_2\text{---COOH}\cdot\text{H}_2\text{O}$ 3:4:5:1, occurs combined as tannins in hundreds of plants. It can be prepared by boiling tea or tannin with dilute acids, and it can also be made in the laboratory by several methods. It consists of colorless or slightly yellow crystals that have a limited solubility and are slightly astringent in taste. It is a strong reducing agent, giving a precipitate of metallic silver when warmed with ammoniacal silver nitrate. Ferric salts yield a bluish-black precipitate, but excess of reagent forms a green solution. Bismuth Subgallate N.F. (Dermatol) is a basic, insoluble salt.

Gallic acid is used in the manufacture of dyes but mostly for making ink. When a solution of the acid is treated with ferrous salts, no color is obtained at once, but a blue-black is gradually formed by oxidation. Acids are added to retard this process, but paper upon which such an

ink is used neutralizes the acid, and a blue color is formed on it. In order to get this at once, a blue dye is usually added. Oxalic acid will remove fresh gallate-ink stains, but hypochlorites are needed for the dye.

Tannic Acid U.S.P. (Gallotannic Acid, Tannin) is usually obtained from nutgall and occurs also in other plants. Although the product from nutgall is fairly uniform, the composition is always somewhat variable. Upon hydrolysis with dilute acids, it gives gallic acid and glucose in variable amounts, and it is presumed on other grounds that it is pentadigalloyl-glucose. A synthetic compound from m-digallic acid



proved to have similar properties but was not identical.

Tannic acid consists of colorless to light-brown crystals that are very soluble in water and have a strongly astringent taste. It gives with ferric salts a blue-black color or precipitate and also yields precipitates with many alkaloids, starch, some proteins, and gelatin. It is used in medicine, in the laboratory as a reagent, as a mordant in dyeing, and in the manufacture of gallate-inks.

In order to mask the astringent action and make it develop gradually in the gastro-intestinal tract, several derivatives are employed in medicine. Acetyl tannic Acid (Acetannin) and Albumin Tannate (Albutannin) are the most popular of these. Protan is a combination with casein. The various tannin-containing drugs give the same effects but more slowly.

Tannins, generally, are probably much like gallotannic acid, being all astringent substances that hydrolyze to gallic, catechuic, or similar acid and a sugar. They are amorphous or crystalline, dissolve readily in alcohol or ethyl acetate but variably in water, and are all reducing agents. They are found in many plants, where the amount is determined by titration with permanganate before and after precipitation of the tannin. Some of these plant materials are used in medicine for the "masked" tannin they contain; included are kino, nutgall, krameria, and gambir.

With respect to the tanning of hides, there are two classes of these substances—bloom tannins and non-bloom tannins. The former, like the official tannic acid, give a blue-black color with ferric salts, precipitate gelatin-salt solution, produce a bloom on animal skins, and are precipitated by powdered hide. Consequently, they are useful in the making of leather. The chief materials used for this purpose are oak-bark, sumac, and chestnut. The non-bloom types occur much more widely, and most of the tannin-drugs like catechu, kino, krameria, and gambir are in this class. They produce a green color with ferric salts and yield a precipitate with gelatin-salt solution, but do not give a bloom to hide. They can be further distinguished in the laboratory by the fact that they hydrolyze to catechuic and other acids, but not gallic.

REVIEW QUESTIONS

1. State five methods for making phenolic acids and write equations to illustrate each.
2. Write equations for the Kolbe synthesis. How could the para compound be obtained chiefly?

3. Why is salicylic acid dibasic? Why does it color ferric chloride? What is meant by true salicylic acid?
4. Write equations for producing sodium salicylate and disodium salicylate from the acid.
5. Name the six official salts of salicylic acid. Which of these are soluble in water?
6. Write formulas of methyl and ethyl salicylates and of the carbonate of the latter.
7. How is salol made? What happens to its sodium salt when heated? Write equations.
8. Why must aspirin be protected from moist air? Write equation for its hydrolysis.
9. Salicylic acid is a cyclic anhydride. Write the formula.
10. From what acid is coumarin derived? What is its geometric isomer called? Write the formulas.
11. Show by formulas the relation between tyrosine, tyramine, iodogorgoic acid, and thyroxine.
12. Write the formulas of catechuic, veratric, vanillic, caffeic, and piperic acids.
13. What is the source of gallic acid? How is it used in making inks? What is dermatol?
14. What substances are obtained from tannic acid on hydrolysis? What is supposed to be the composition?
15. What is meant by "masked" tanain? Name two chemical and two natural products which contain masked tanain.

Name _____

CHAPTER XXXIII

CONDENSED NUCLEI

NAPHTHALENE

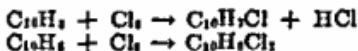
It was earlier stated that naphthalene is the chief constituent (about 6 per cent) of coal tar. This is practically the only source for the compound, although it can be obtained also by the destructive distillation of many other natural materials or by pyrolysis of ethylene, alcohol, ether, acetic acid, camphor, etc. Furthermore, it may be synthesized by heating phenylbutylene or the addition product from it by bromine. The empirical formula is $C_{10}H_8$, so it must be produced from phenylbutylene by loss of 2 hydrogen atoms.



Naphthalene is a colorless solid with a characteristic odor that is familiar to all of us as old-fashioned moth balls. It melts at 80° and boils at 218° , but its vapor pressure is very high, so that it is readily sublimed and can be distilled with steam. It is insoluble in water, but dissolves easily in ether, hot alcohol, and other solvents. The substitution products of naphthalene are exceedingly important in industry, and practically all of them are made from the hydrocarbon. The high value of these is reflected in the production and use of more than 100,000,000 pounds annually.

Reactions.—In chemical properties naphthalene is very similar to benzene, but with notable differences in some respects.

1. Halogens will substitute or add in exactly the same way but with less difficulty.



When addition takes place, each molecule readily takes up 2 and 4 atoms of halogen.



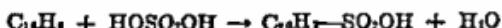
Three more pairs of halogen atoms can still be added, but to bring this about is no easier than in benzene.



2. Nitric acid produces nitration in the same manner as with benzene, and again we find this easier to do.



3. Sulfuric acid also acts with greater readiness to yield sulfonic acids.



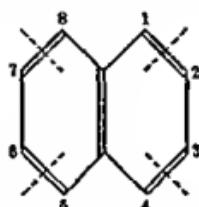
4. Sodium alcoholate, which has no effect on benzene, is effective in adding 2 atoms of hydrogen and 2 more can be added with hydrogen and a nickel catalyst, $C_{10}H_8 \rightarrow C_{10}H_{10} \rightarrow C_{10}H_{12}$. Any further reduction requires agents that are energetic enough to act with benzene, when 6 more atoms will add to give $C_{10}H_{18}$.

5. Oxidizing agents that will not affect benzene at all convert naphthalene quite readily to phthalic acid or its anhydride.



6. Finally, the substitution of hydrogen can be accomplished by the Friedel-Crafts reaction exactly as with benzene.

Structure.—Oxidation to phthalic acid shows that naphthalene has a benzene ring. If nitronaphthalene is treated in the same way, o-nitrophthalic acid is the chief product, whereas if the same nitro compound is first reduced to aminonaphthalene, the oxidation gives phthalic acid as before. These effects demonstrate fairly conclusively that the hydrocarbon must have two benzene rings with two common carbon atoms.



In nitronaphthalene the unsubstituted ring breaks, while in the amino compound the split occurs in the substituted ring, in each case at the points indicated by the dotted lines. When 4 halogen or 4 hydrogen atoms have been added, obviously we now deal with but one benzene ring and side-chains, showing why further addition requires more energetic action. Many syntheses of naphthalene derivatives from those of benzene furnish incontrovertible evidence for the formula selected. Actually there is no benzene ring at all in the molecule and no resonance, since the bonds cannot be shifted. Not until the first double bond is removed by addition does the resonance of benzene develop, showing why hydrogen or halogen can react easily.

Substitution.—For any 1 radical there are 2 mono compounds, referred to generally as alpha and beta. These are also numbered as in the formula, and it is obvious that 1,4,5, and 8 are all alike but different from 2,3,6, and 7 which are also alike. These positions when occupied once are alpha and beta respectively. With two substitutions of identical radicals there are ten possibilities: (1-2), (1-3), (1-4), (1-5), (1-6), (1-7), (1-8), (2-3), (2-6), and (2-7). If they are unlike radicals, 14 compounds can be formulated. The number of possibilities for three and more substitutions becomes proportionately greater, but we need not carry the discussion of this subject any further here. It is said that 8 unlike groups could be introduced in different ways to give several millions of compounds.

When naphthalene is acted upon by halogenation or nitration, the first product is an alpha compound. Sulfonation, however, results in either alpha or beta substitution, depending on temperature. Below 80° the alpha compound is almost the sole product, while above 160° all is converted to the beta, and at intermediate temperatures a mixture is obtained. Alphanaphthalenesulfonic acid changes to the corresponding beta compound at about 120°.

With one substituent already present, a modified but less definite Crum-Brown rule prevails. If this be ortho-para-directing and present in alpha

CONDENSED NUCLEI

position, the second action takes place as in benzene in 2 (ortho) or 4 (para). If in beta position, the new group goes in 1 (ortho) or in the second ring (para). When the radical already present is meta-directing, the second substitution usually takes place in the second ring.

Tetralin, tetrahydronaphthalene,



is made by reducing the hydrocarbon with hydrogen and a nickel catalyst. Decalin, the completely reduced molecule and entirely an alicyclic compound, is produced by more powerful agents. Both compounds are high-boiling liquids that are used as solvents.

Alphanaphthalene, obtained by direct nitration, is a solid melting at 59°. It is used chiefly for conversion to the corresponding amine in the manufacture of dyes. The beta compound is of much less importance, since it must be made indirectly from the amine.

Both of the amines are much used in the manufacture of dyes and as antioxydants. The beta derivative can be prepared by treating the corresponding hydroxy compound with ammonia and ammonium sulfite. In both amines the amino group can be hydrolyzed to hydroxyl by heating with a solution of sodium bisulfite. Alphanaphthylamine hydrochloride is an official reagent, as is also betanaphthylamine acetate. Naphthionic acid, $C_{10}H_8(NH_2)SO_2OH$ 1:4, prepared by heating alphanaphthylamine sulfate, is very useful in the dye industry. It is different as a sulfonic acid in being insoluble in water. The tetrahydro derivatives of these amines are also articles of commerce.

Betanaphthol U.S.P., $C_{10}H_8OH$, is very much like phenol in physical and chemical properties, although it is very much less soluble in water. Its ammonium salt exhibits a slight, bluish fluorescence, and ferric chloride gives a green color. It is prepared on a large scale from the sulfonate, chiefly for the production of azo dyes by coupling in position 1 with diazonium salts; if the position is occupied, no coupling takes place. Bismuth Betanaphtholate (Orpbol) is insoluble and like other bismuth compounds. Betanaphthyl Benzoate (Beazonaphthol) and other esters as the salicylate (Betol) are very much like salol and used in about the same way. The ethyl ether is employed in perfumery as Nerolin.

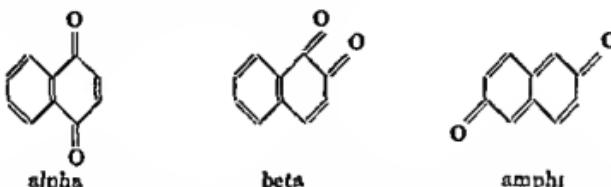
Many derivatives of betanaphthol are known, most of them dyes or dye intermediates. Some will be discussed in a later chapter, and we can mention only a few of them here. Aluminol, aluminum betanaphthol-sulfonate, $[C_{10}H_8(OH)(SO_2O)_2]_3Al_2$, has been used as an antiseptic. Eikonogen, a photographic developer, is sodium aminobetanaphtholsulfonate. Among the dye intermediates are R-salt, the sodium salt of the 3,6-disulfonic acid, and G-salt, the corresponding 6,8 compound. Among the dyes that will be mentioned again are orange II, scarlet red, and scarlet red sulfonate. 1-Nitrosobetanaphthol is used as a reagent for cobalt.

Alphanaphthol is also produced from the sulfonate, although it can easily be made in the laboratory by diazotization of the amine. It is more poisonous than the beta compound but is similar in most other respects. It can be distinguished by the violet color with ferric chloride and the production with sodium hydroxide and iodine of a violet color which beta-

naphthol does not give. As will be recalled, alphanaphthol is used in the Molisch reaction for carbohydrates. Coupling with a diazonium salt takes place only in position 4 to produce important dyes like orange I. Martius' yellow and naphthol yellow-S are other dyes that will be mentioned again. Chromotropic acid, an official reagent, is 1,8-dihydroxynaphthalene-3,6-disulfonic acid, and 1-amino-2-naphthol-4-sulfonic acid is also employed as reagent.

Naphthoic acid or α -naphthalenecarboxylic acid and naphthalic acid, naphthalene-1,8-dicarboxylic acid, are dye intermediates.

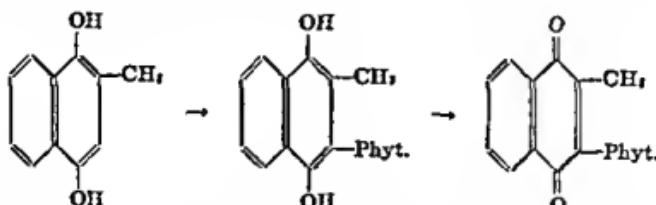
Naphthalene forms quinones that are analogous to those of benzene, that is 1,2 and 1,4, and in addition another in the 2,6 position. These are called respectively alpha, beta, and amphi.



Alphanaphthoquinone, produced by oxidizing naphthalene with chromium trioxide in acetic acid, is a yellow solid. Betanaphthoquinone, prepared by oxidation of 1-aminobetanaphthol or the dihydroxy compound, is orange, as is also amphinaphthoquinone, made by oxidizing 2,6-dihydroxynaphthalene.

Vitamin K₁, which seems to be essential to the proper coagulation of blood, is a derivative of alphanaphthoquinone. It was first discovered in alfalfa and for some time this was the only source. Active work in several laboratories succeeded in indicating its structure as 2-methyl-3-phytylalphanaphthoquinone, and its synthesis was reported in two independent papers in 1939. For this was necessary the compound, phytol, C₂₀H₃₈OH.

The synthetic process for vitamin K₁ involves the interaction of 2-methyl-1,4-naphthohydroquinone and phytol in dioxane with oxalic acid, or phytol bromide, and subsequent oxidation to the quinone by silver oxide in ether.

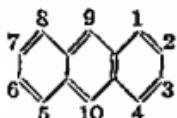


Meadiolae U.S.P., 2-methylnaphthoquinone, has similar physiological action and is possibly an active form during metabolism.

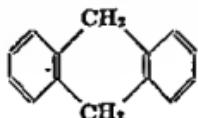
ANTHRACENE

In the higher boiling fractions of coal tar is found another hydrocarbon, anthracene, that was once an important crude material for making several useful dyes. Today, however, the intermediates needed are largely made from benzene derivatives, and anthracene is becoming less valuable.

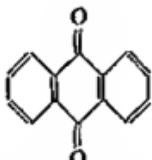
The hydrocarbon, $C_{14}H_{10}$, is a colorless solid with a bluish fluorescence. It is very easily attacked by reagents such as nascent hydrogen or oxygen and also by the typical agents for aromatic compounds generally. The one of these actions that is of importance is its easy oxidation to anthraquinone, the basis for preparation of the useful derivatives. The two acceptable formulas for anthracene are given, but the one on the left best expresses its properties and is usually preferred. The point of attack by



reagents is at 9 and 10, where halogens, hydrogen, or oxygen may enter the molecule. Thus, reduction with sodium amalgam produces $C_{14}H_{12}$ or

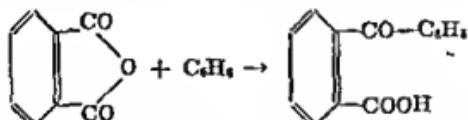


Anthraquinone

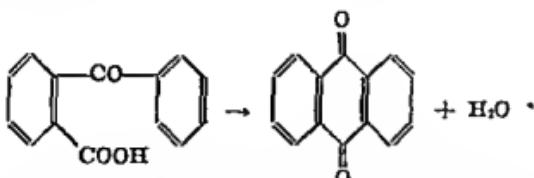


is the most important derivative of anthracene, from which it can be produced by action of a variety of oxidizing agents. It has been found much more convenient, however, to make the quinone from phthalic anhydride and benzene, because the dyes that are manufactured from the product are less liable to be contaminated and are better in other ways.

The synthesis is carried out in two steps. In the first, benzene and the anhydride condense in the presence of aluminum chloride to o-benzoylbenzoic acid.



In the second step, this is treated with concentrated sulfuric acid, when the center ring is closed.

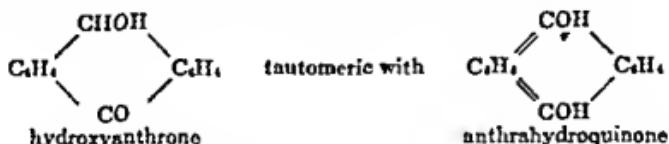


Substituted compounds can be prepared in the same way by starting with the appropriate derivative of benzene or of phthalic acid.

Anthraquinone is a yellow solid that is not volatile with steam and does not dissolve in most solvents. Warm sulfuric acid will form a solution, from which the quinone may be separated by dilution, an excellent

method of purification. When heated to a high temperature with sulfuric acid, it is sulfonated in beta (2) position, but if mercuric sulfate is used as a catalyst, the reaction can be carried out more easily and gives practically entirely the alpha (1) compound. Fusion of these sulfonates with alkalies results in the corresponding hydroxyl derivatives, and the amines can be made from the last by heating with ammonia under pressure.

Reduction of anthraquinone or its substitution products leads to a number of interesting compounds. While substances like sulfur dioxide or hydrogen iodide, which easily affect benzoquinone, will not act on them, the changes can be brought about by a variety of other agents. For example, zinc and ammonia add 2 hydrogens at 9 or 10 to give



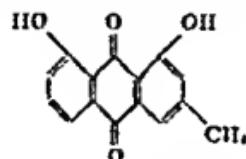
Other reagents give a disemicarbazide alcohol that is not known but dehydrates to



and finally anthracene. The most interesting of these are the anthrahydroquinones that are obtained by action of sodium hydrosulfite, Na₂S₂O₄.

Alizarin, 1,2-dihydroxyanthraquinone, occurs as a glycoside in the madder root, *Rubia tinctorum*. It is made by fusing the betn sulfonic acid with sodium hydroxide and an oxidizing agent like sodium chlorate. Upon reduction with zinc and ammonia, it forms a desoxy compound that is colorless. Sodium alizarinsulfonate (alizarin carmine) is an official reagent. Anthralin N.N.R., 1,5-dihydroxyanthraquinone, is a synthetic substitute for chrysarobin. Anthragallol, 1,2,3-trihydroxyanthraquinone, has been synthesized from benzoic and gallic acids. Purpurin, another trihydroxy (1,2,4) derivative, is found in madder.

A number of the so-called anthraquinone drugs, including cascara, frangula, aloe, chrysarobin, senna, rhubarb, and rhamnus cathartica, yield a substance known as chrysophanic acid, sometimes called methylalizarin. This is 4,5-dihydroxy-2-methylanthraquinone,

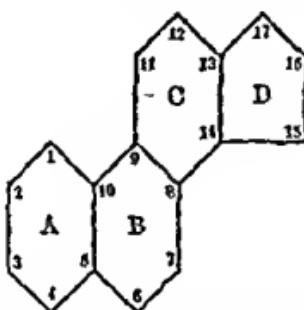


The hydroquinone, or desoxy compound, obtained by reduction and called chrysophanol, is presumed to be the chief constituent of Chrysarobin U.S.P., although the formula is often given as C₁₉H₁₈O₄, which is equivalent to 2 molecules of chrysophanol plus 1 molecule of water. The therapeutic action of chrysarobin is attributable to its easy oxidation to chrysophanic acid.

CHAPTER XXXIV

CONDENSED ALICYCLIC

SEVERAL important substances of the alicyclic group were not considered in Chapter XXIII, because they contain condensed nuclei like naphthalene and anthracene, in some cases partly aromatic. First, we need to discuss a series of very useful compounds that are derived from a common pattern of phenanthrene condensed with cyclopentane, the so-called cyclopentanophenanthrene nucleus, $C_{17}H_{26}$.*

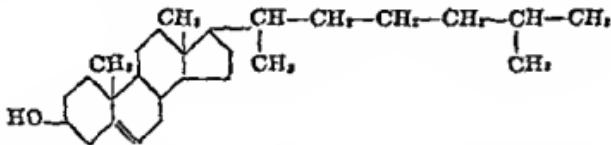


The various classes that have this common pattern are: the sterols; bile acids; vitamin D; the estrogens; the androgens; the cortical hormones; aglucones of the digitalis group and some saponins.

STEROLS

The sterols are monatomic alcohols that are very widely spread throughout the animal and vegetable kingdoms associated with fats. They apparently differ very little in structure and all have the pattern of cyclopentanophenanthrene.

Cholesterol, $C_{27}H_{44}O$, the most common of the sterols, is derived from this pattern by substituting methyls at 10 and 13, hydroxyl at 3, and a branched octyl radical at 17, and putting a double bond at 5.



It occurs very widely in animal fats and can be separated from them in colorless crystals melting at 148° to 151° and insoluble in water. With digitonin it gives a white precipitate. Upon reduction, the hydroxyl group and the double bond are removed to give a hydrocarbon, $C_{27}H_{46}$, that is called cholestane. This oxidizes with chromic acid to allocholanic acid, $C_{27}H_{42}COOH$, by oxidizing off the isopropyl group.

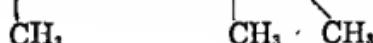
Wool Fat U.S.P. and Hydrons Wool Fat U.S.P. (Lanolin) are certainly not fats and probably should not be called waxes as is often done. They

* The author for convenience calls this hydrocarbon "Sterane" and refers the names of other compounds to it; e. g., estrane is 13-methylsterane.

contain chiefly cholesterol, together with some esters of it with the fatty acids, stearic, palmitic, and oleic.

Coprosterol, $C_{27}H_{46}O$, found in the feces, is shown to be a dihydro derivative of a geometric isomer of cholesterol. It reduces to coprostanone, $C_{27}H_{48}$, isomeric with cholestanone. Upon oxidation with chromic acid, it forms cholanic acid, a geometric isomer of allocholanic acid.

Ergosterol, $C_{28}H_{44}O$, differs from cholesterol in having another double bond at 7 and the nonylene side-chain, —CH—CH=CH—CH—CH—CH₃,

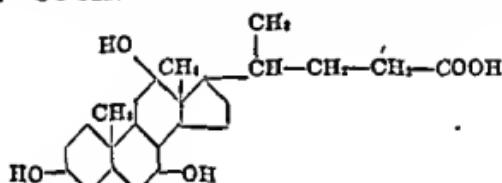


at 17 in place of the saturated octyl. It is found in yeast and ergot and is important because of its relation to vitamin D.

Other sterols are quite numerous, but each presumably differs very little in structure from cholesterol. They are usually named as sterols, with a prefix to indicate source. Illustrations of these are stigmasterol and daucosterol. In general the vegetable substances of this class are called phytosterols.

BILE ACIDS

The acids of animal bile are taurocholic and glycocholic acids, combinations respectively of cholic acid with the amino acids, taurine and glycine. Cholic acid itself, $C_{24}H_{40}O_5$ or $C_{24}H_{38}(OH)_3COOH$, is derived from the fundamental hydrocarbon by substituting three hydroxyl groups at 3, 7, and 12, two methyl groups at 10 and 13, and at 17 the radical —CH(CH₃)—CH₂—CH₂—COOH.



It reduces to cholanic acid, stereoisomeric with allocholanic acid from cholestanone, by losing the three hydroxyls. The carboxyl group can also be reduced to give cholang, $C_{24}H_{42}$.

Lithocholic acid occurs in human bile and to a small extent in Ox Bile U.S.P. It differs from cholic acid in not having the hydroxyl groups at 7 and 12.

Dehydrocholic Acid N.N.R. (Decholin) is an oxidation product of cholic acid, each of the three hydroxyls being changed to ketones. This is equivalent to removing 6 atoms of hydrogen, hence the name.



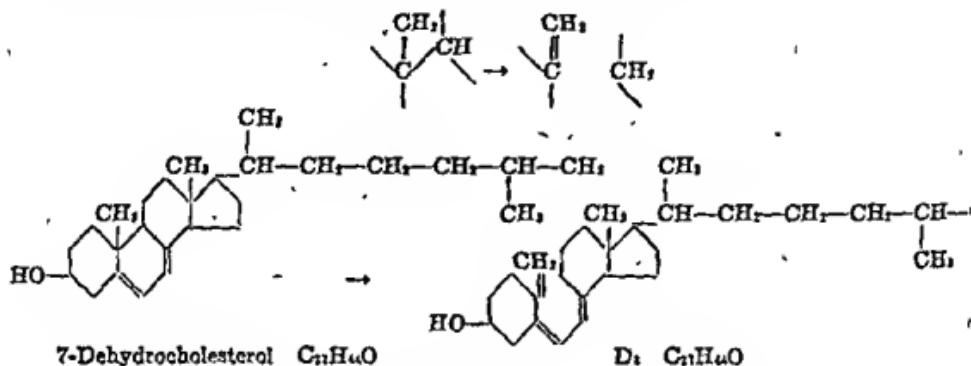
Sodium Dehydrocholate N.N.R., the sodium salt, is used in the same way.

VITAMIN D

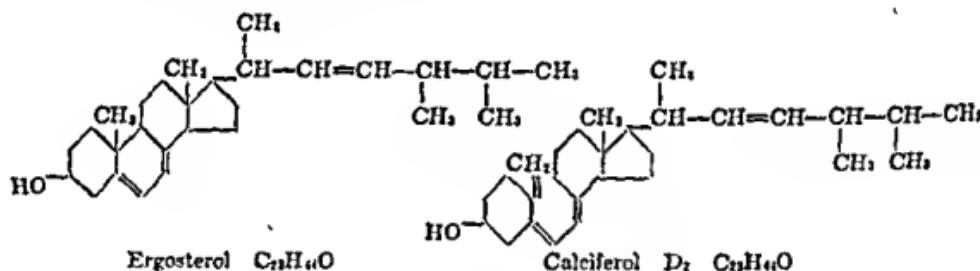
The original fat-soluble vitamin of cod liver oil was shown to be a mixture of A and D just about the time it was demonstrated that ultraviolet light cures rickets, and very little later it was proved that irradiated foods are antirachitic. By careful experimentation the substance responsible for the effect was found to be the sterol, and it was soon demonstrated that

the irradiation of ergosterol, present in the sterols to a small extent, changed it to several substances that are more or less antirachitic. The most important compound so formed is calciferol or vitamin D₂. The natural D₃ in fish liver oils is different and can be formed by irradiating 7-dehydrocholesterol. The formerly recognized D₁ is now known to be a mixture.

The change that takes place by exposure to ultraviolet light is disruption of the ring at 10 by migration of a hydrogen:

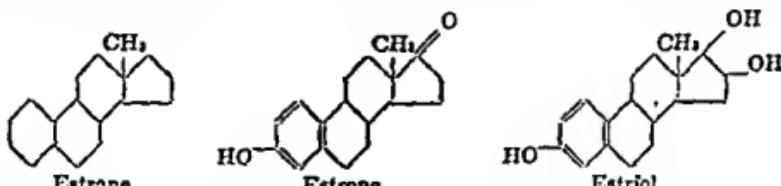


Undoubtedly the irradiation of many other substances will yield antirachitic compounds, but at present the only substances that are recognized in Synthetic Oleovitamin D U.S.P. are calciferol (D₂, irradiated ergosterol, viosterol, drisdol) and the natural D₃, made by irradiation of 7-dehydrocholesterol.



ESTROGENS

The estrogenic substances, female sex hormones, are oxidation products of the sterols, but have the same parent hydrocarbon. However, for purpose of naming they are referred to the substance estrane, C₁₈H₂₈, which has a methyl at 13.



Estrone N.N.R. (Theclia), C₁₈H₂₆O₂, is 3-hydroxy-17-keto-1,3,5(10)-estratriene. It is extracted from the urine of pregnancy or from the placenta and is also found in plants.

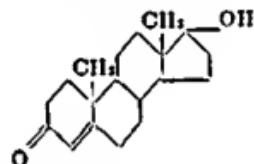
Estriol N.N.R. (Theclol), $C_{18}H_{24}O_3$ or 3,16,17-trihydroxy-1,3,5(10)-estratriene, is also extracted from the urine of pregnancy. It is much less active physiologically than estrone. Upon dehydration estriol is converted to estrone; water is abstracted from H at 17 with OH at 16 giving $-CO=CH-$, an enol of $-CO-CH_2-$ which is estrone.

Quite a number of other estrogenic substances have been isolated from other sources and manufactured synthetically. Some of them are derived from estrane but with more unsaturation in ring B, as for example, equilin, equilenin, and hippulin from mare's urine. From sows' ovaries is obtained Estradiol U.S.P., 3,17-dihydroxy-1,3,5(10)-estratriene, which is the most powerful of the group. More prolonged action is obtained by using the benzoic or propionic esters, as in Estradiol Benzoate U.S.P., in which esterification is on the hydroxyl group at 3. Among the synthetic substances, which have no relation structurally, are diethylstilbestrol and octofollin (Chapter XXVII).

ANDROGENS

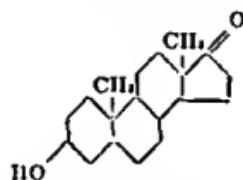
The male sex hormones or androgens, isolated from male and female urine and from testicular extracts, are derived from androstane, $C_{19}H_{28}$, which is 10-methylestrane. Several such substances have been found, and all of them are closely related, contrasted with the variety of estrogenic compounds.

The most powerful member of this group is testosterone, $C_{19}H_{28}O_2$ or 3-keto-17-hydroxy- Δ^4 -androstene.



It was first obtained from testicular extract but has been synthesized.

Androsterone, $C_{19}H_{28}O_2$, obtained from male urine or synthesized from cholesterol or stigmasterol, is 3-eis-hydroxy-17-ketoandrostane.



Dehydroisoandrosterone, $C_{19}H_{28}O_2$, which is only about one-third as active, has a double bond at 5 and is a trans compound at the hydroxyl group.

Pregnadiol, $C_{19}H_{28}O_2$, differs from androsterone in having the group, $CH_2-CHOH-$, substituted at 17 in place of the ketone. It is physiologically inactive and probably an excretion product of progesterone.

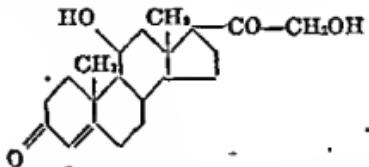
Progesterone (progesterin, corporin, luteosterone), $C_{21}H_{30}O_2$, is a female sex hormone from the corpus luteum. It was first isolated in the crystalline state in 1931 and was shortly afterward synthesized. While it has none

of the character of the androgens, it is closely related to testosterone chemically, having an acetyl at 17 in place of hydroxyl. Two forms of it are recognized, alpha melting at 128° and beta melting at 121°.

ADRENAL CORTEX

From the crude extract of the adrenal cortex, several closely related hormones have been isolated. They are very much like progesterone in structure and all are derived from androstane. In addition, several synthetic substances have been reported which are very similar chemically to the hormones. How many of these may be useful in medicine it is difficult to state at present writing.

Corticosterone, the first that was investigated and probably the prototype, is a dihydroxyprogesterone.

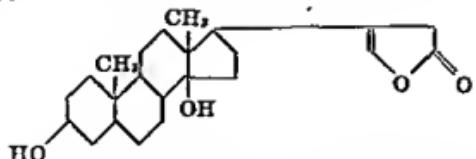


Others of the series have a ketone group at 11 or no hydroxyl there at all. In some of the synthetic compounds, hydroxyl has been introduced at 17 in addition to the group given in corticosterone.

DIGITALIS AGLUCONES

The group of drugs that act like digitalis on the heart contain glycosides, whose chemistry until recently has been almost entirely unknown. As a matter of fact, even the substances present in these drugs have been but imperfectly known. Whenever a substance was isolated in a more or less pure state, it was given a name and its products of hydrolysis, usually quite conglomerate, were determined partly. Digitalis, for example, is known to contain one or more glycosides whose identity is uncertain. During the extraction of at least one of these, hydrolysis takes place to split off acetic acid and d-glucose, and the substance actually isolated is digitoxin.

Digitoxin hydrolyzes to a modified aldohexose, digitoxose, and a sugarless substance or aglucone, digitoxigenin, $C_{23}H_{34}O_4$. This is derived from androstane by substituting hydroxyls at 3 and 14 and an unsaturated lactone ring at 17.



In the same way several other aglucones have been isolated from digitalis, strophanthus, squill, convallaria, etc. Gitoxigenin differs in having another hydroxyl at 16, while digitaligenin is derived from it by dehydrating to give double bonds at 8(14) and 15. Digoxigenin has hydroxyls at 3,11,

and 14 and strophantidin has an aldehyde group in place of methyl at 10, and hydroxyls at 3,5, and 14. Several others of the group are known to have similar structure.

Substances from skin glands of certain toads have physiological action like digitalis; *e. g.*, bufotoxin. Although they are not glycosides, they can be hydrolyzed to compounds that have a structure very similar to that of digitoxigenin.

SAPONINS

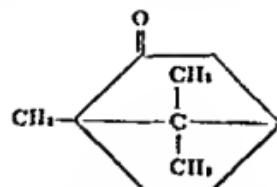
A number of non-nitrogenous glycosides of widely different origin are grouped together under the name of saponins. They occur in more than 400 species of plants belonging in at least 50 families. Several drugs that have been used with some success for years probably owe most of their effects to saponins; in this class are sarsaparilla, seneca, caulophyllum, guaine, and dioscorea. In addition, some of our drugs contain saponins as minor ingredients, such as digitonin of digitalis and adonic acid of adonis. The only properties that saponins possess together, besides those of glycosides in general, are those of making a foam in water and of hemolyzing blood.

A few aglucones of saponins that have been investigated carefully have also been found to contain the cyclopentanophenanthrene structure. The methyl groups at 10 and 13 and the hydroxyl group at 3 are again a feature. Some others have an entirely different make-up, and this might be expected in so conglomerate a group of substances. Nevertheless, the sterol pattern has been found in more than one genus, and the probabilities are that many saponins are closely related to the sterols, sex hormones, and cholic acid. It might be added that the compounds of different structure are like the sesquiterpenes, which appear to be degradation products of the sterols.

OTHER COMPOUNDS

All of the bicyclic terpenes have condensed rings. For example, pinene (Chapter XXIII) has one four- and one six-membered ring. Others are betapinene, camphene, carenes, thujene, sabinaene, and fenchene.

In addition, several derivatives of these are important. Camphor U.S.P., $C_{10}H_{16}O$, which has the formula

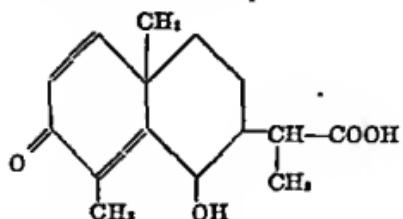


is dextro as obtained from camphor oil but is racemic if synthetic. Derivatives used in medicine are Monobromated Camphor N.F. and Bismo-Cymol N.N.R., a basic bismuth camphocarboxylate. The secondary alcohol corresponding to camphor, borneol, is present in many volatile oils, notably in the official ones of rosemary and dwarf pine-needle.

The sesquiterpenes and polyterpenes are mostly compounds with con-

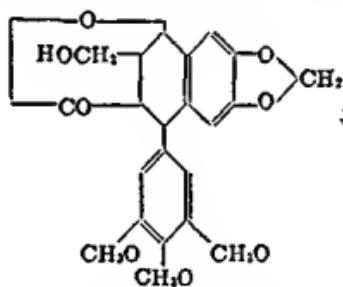
densed rings. The exact structures of cadinene and of several others have been determined, also those of various sesquiterpene alcohols.

Santonin U.S.P., $C_{15}H_{18}O_3$, is the inner anhydride of santonic acid.



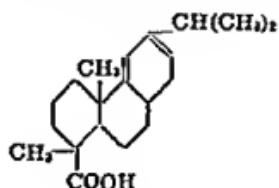
It forms colorless crystals that rapidly become yellow on exposure to light although stable in the air. It is almost insoluble in cold water and not very soluble in alcohol, but it will dissolve in boiling dilute alkali. The formula contains 2 asymmetric carbon atoms, a levo form being the natural one.

Two of the substances found in podophyllum are also lactones. Podophyllotoxin, $C_{22}H_{22}O_8$, the drastic ingredient, probably has the structure



Picropodophyllin, which is physiologically inactive, is isomeric, the lactone being with the hydroxyl in $-\text{CH}_2\text{OH}$.

Abietic (sylvic) acid, $C_{20}H_{30}O_2$, the chief ingredient of rosin, is formed from several terpenes by oxidation. On the other hand, it contains the phenanthrene nucleus and may be related to the sterols. It consists of levorotatory, insoluble crystals melting at 171° to 174°.



REVIEW QUESTIONS

1. Write the formulas of the cyclopentanophenanthrene pattern and number the carbon atoms.
2. What structural features has cholesterol in addition? Where does it occur?
3. What is formed on reduction? when the product is oxidized?
4. What is the composition of wool fat?
5. What is the structure of cholic acid? of bile acids? of decholin?

6. What change takes place in ergosterol on irradiation? What is the product?
7. How does the natural vitamin D₃ differ from D₂?
8. Write the formulas of estrone, estriol, and estradiol.
9. How does androstane differ from estrane? Name testosterone as a derivative of estrane and as a derivative of androstane.
10. Write formulas of progesterone and corticosterone.
11. How are the digitalis aglucones derived from cholesterol?
12. Write the formulas of camphor and borneol. In what official oils is the latter found?
13. Write the formula of santonin. Why does it dissolve in alkalies? What effect has light on it? Which of the carbon atoms are asymmetric?
14. Where does abietic acid occur? Why can it be said to be related to the sterols?

CHAPTER XXXV.

VOLATILE OILS

IN numerous instances we have noted compounds of various kinds which were at that time described as being found in volatile or essential oils. Indeed, the student cannot have failed to conclude that these oils have a heterogeneous composition. Because they are quite prominent in medical and pharmaceutical practice, it will not be out of place at this point to make a general survey of the matters of interest in this field. Incidentally, the terpenes and their oxygenated derivatives are probably related to the sterols and some hormones and vitamins.

The oils occur in plants of practically all families, either free in vittæ and between cells or combined in glycosides. Whether they are to be considered storage forms, transport media, or excretions, or serve some other function has not been demonstrated, but many plant physiologists prefer to think that they are waste products from plant metabolism. As has been noted, they may be formed by degradation of hormones, vitamins, and related substances.

They are prepared from the plants or their parts by steam-distillation, dry distillation, extraction, or pressing. Of the official oils, all are obtained by the first method, except those from the citrus fruits, which are expressed. Those from fragile flowers, such as jasmine, violet, and hyacinth, are extracted for use in perfumery by a volatile solvent or, more often, by a non-volatile one like lard.

The general composition of a particular oil varies more or less with season of the year, climate, soil, method of cultivation and preparation, and with other factors. From an ultimate analysis, we find only carbon, hydrogen, and oxygen, and occasionally nitrogen and sulfur. Yet the kinds of compounds are very numerous, since almost every class that we have discussed so far for these five elements is represented.

In examining a new oil, or samples of a known one, the physical constants are first ascertained, because they often throw much light on composition or purity. The specific gravity may vary from 0.7 to 1.3; values below 0.9 indicate lower alicyclic hydrocarbons, between 0.9 and 1.0 shows oxygenated compounds or higher alicyclic hydrocarbons, while above 1.0 means aromatic substances, nitrogen, or sulfur. The index of refraction is high with much unsaturation and when the oil contains nitrogen or sulfur. Practically all of the oils are optically active, although little can be judged from the amount because racemic mixtures are also present. The melting or solidifying point is not definite, but solids or stearoptenes often precipitate on cooling and can be separated from the oleoptene. The boiling point range is usually above 150° and may run up to more than 300°. The first substances that come over at 150° to 190° are terpenes, at 190° to 225° oxygenated terpenes, 225° to 275° aromatic and sesquiterpenes, above 300° polyterpenes. Finally, the solubility in alcohol of various dilutions is usually specified for individual oils as a guide to determining purity. Most of them are soluble in absolute alcohol and insoluble

in water, so that mixtures of the two solvents can be used to test the limits of solubility.

Certain chemical values are also of aid in determining purity and are specified in official assays. These are likewise of much help in indicating the kind and amounts of ingredients in a new oil. The acid, ester, and saponification numbers as applied to fats are important, because acids and their esters are of frequent occurrence. The alcohols in general are estimated by saponification after esterifying with acetic anhydride or formic acid. The phenols, together with the acids which can be subtracted, are measured by dissolving in dilute alkali and noting the decrease in volume. Ketones and aldehydes may be converted to oximes by hydroxylamine or to hydrazone, in which case excess of reagent is found by titration. One may also get the ketones and aldehydes by dissolving in solution of sodium bisulfite and noting the decrease in volume of oil, because bisulfite forms soluble addition products. Finally, nitrogenous bases may be extracted by acids and determined by titration or by precipitation as double salts.

In considering the individual compounds found in oils, it is impossible to make more than a brief survey. Over 450 substances have been identified and, while many of them are but minor ingredients or are found only in rare oils, yet the common, widely spread components are varied. We will take each class in turn, noting a few of the most important representatives and those that are the chief ingredients of official oils or of ones that are commonly used. In order to emphasize the diversity of composition and to call attention to some of the compounds, a table of the official oils is given later, with a few of the important components that have been identified.

HYDROCARBONS

Aliphatic.—Many oils give a stearoptene that proves to be almost entirely paraffin, probably coming from the bloom on leaves and fruit. This is particularly true of fresh rose oil, to a lesser extent of sassafras and neroli. In one or two instances an individual compound like triacontane has been isolated. Oils from oleoresin of the Jeffrey pine and of *Pinus sabiniana* are almost wholly n-heptane. Olefines are represented by several compounds; octylene in lemon and bergamot is an illustration.

Terpenes are, of course, the main hydrocarbons. Limonene is the chief component of orange and lemon and is found also in about half of the official oils. α -Pinene, the most widely occurring of all ingredients, is practically the sole compound in turpentine and is contained in most others that are used in pharmacy. In addition there are many other terpenes that have been characterized. Among the monocyclic are dipentene (dl-limonene, α -phellandrene, β -phellandrene, α -terpinene, and γ -terpinene). The most important dicyclic terpenes are β -pinene, camphene, sabinene, and the carenes. Santene, C_9H_{16} , and nortricycloeksantalene, $C_{11}H_{18}$, are closely related to them.

Aromatic.—The most important is cymene, found in several of the official oils and in many others. Its relation to thymol and carvacrol has already been pointed out. Benzene, toluene, the xylenes, and naphthalene are sometimes encountered, while styrene is an ingredient of the product from storax.

Sesquiterpenes.—The structural formulas for some of them have been worked out, but aside from showing their relation to isoprene and the sterols, no useful purpose would be accomplished in presenting them here. The most common is cadinene which is dicyclic and contains two double bonds; it adds hydrogen chloride to form $C_{15}H_{24} \cdot 2HCl$. The name is derived from the official oil of cade, now known as juniper tar. Bisabolene of lemon and bergamot and zingiberene of ginger are monocyclic, while santalene is dicyclic and cedrene of cedar oil is tricyclic.

ALCOHOLS

Aliphatic.—Most of these occur as esters, although some of the ones with high boiling points are found partly in the free state. The saturated compounds are well represented, some of the more prominent being methanol, ethanol, isobutyl alcohol, isoamyl alcohol, amylmethylcarbinol, amylethylcarbinol, n-nonyl alcohol, and heptylmethylcarbinol.

In the unsaturated group we find the tertiary linalol (linaloöl), whose acetic ester is an important ingredient of lavender and coriander. The closely related, primary geraniol is of very common occurrence and will be noted as a component of several official oils. Its stereoisomer, nerol, receives its name from neroli (orange flower), of which it is one of several alcohols. The distillation of many green plants, and consequently of various oils, gives β, γ -hexylenic alcohol (2-bexenol), probably a transition product in vegetable metabolism.

Alicyclic.—Menthol is the chief ingredient of peppermint and other of the mints, some of it being in the form of esters. Borneol, closely related to camphor, exists in the free state but is usually found as acetate or other ester; the acetate is prominent in the oils of rosemary and pine-needle. Terpineol, or an ester of it, is found quite widely, especially in cardamom and bergamot. As a useful agent in perfumery, it is usually prepared by hydration of turpentine oil. Other terpenic alcohols of some note are terpinenol-4, dihydrocarveol, fenchol, verhenol, and carveol.

The santalols (alpha and beta) constitute more than 90 per cent of the product from sandalwood. Many other sesquiterpene alcohols have been characterized, among which might be mentioned nerolidol, farnesol, cedrol, eudesmol, and gloholol.

Aromatic.—These are found chiefly in the flower oils where they contribute much to the delicate odors. Benzyl alcohol is one of the most widely occurring and is notable in oil of neroli. Phenylethyl alcohol, which is usually known in commerce as "rose oil," lends its aroma to the products from rose and orange flowers but is not the principal component of either. Others are anisic alcohol, cuminol, phenylpropyl alcohol, and cinnamyl alcohol. Furfuryl alcohol and its methyl derivative are found in clove oil.

ALDEHYDES

Aliphatic.—Formaldehyde, acetaldehyde, and other soluble members of the saturated group are often found in the aqueous distillate and, hence, in the crude oils. Butyric, valeric, isovaleric, caprylic, decylic, and lauric aldehydes are fairly common. The olefinic compounds are represented by citral, the chief odorous ingredient of lemon and orange peels, and citronellal from citronella oil.

Alicyclic.—Peculiarly the aldehyde derivatives of terpenes are seldom encountered and none seems to have been identified in official oils. Myrteal and phellandral are the most important of the few natural ones known.

Many aldehydes of the sesquiterpene class are undoubtedly found, but investigation of them has been limited. Santal oil contains santalal and eksantalal, while cypral, cryptal, and farnesal are others that have been characterized.

Aromatic.—In contrast, aromatic aldehydes are widely spread in many volatile oils. Benzaldehyde is the main ingredient of bitter almond and other kernels of the *Rosaceae*. Cinnamic aldehyde constitutes likewise the bulk of the product from cinnamon and cassia. Among others are p-hydroxybenzaldehyde, anisaldehyde, salicylic aldehyde, cuminal, and dihydrocuminal. The official vanillin is an ingredient of clove oil. Furfural, which is soluble in water, is frequently a product formed during distillation of vegetable matter with steam and consequently is found in the aqueous distillates.

KETONES

Aliphatic.—Again the lower ones are soluble and are, therefore, only in the aqueous portion of the distillates. Acetone and diacetyl are frequently so found; the former is a product from peppermint and the latter from caraway. Amylmethyl, amylethyl, and heptylmethyl ketones are examples of saturated ones found in the oils. Methylheptenone, $\text{CH}_3\text{---CO---CH}_2\text{---CH}_2\text{---CH}=\text{C}(\text{CH}_3)_2$, occurs very widely; for example, it is found in lemon oil.

Alicyclic.—Ketones derived from the terpenes are very numerous and no attempt will be made to give a complete list. Camphor, commercially obtained from oil of camphor or made synthetically from turpentine, is found in many other oils, including those of chenopodium, rosemary, and sassafras. Carvone is the chief ingredient of caraway and spearmint. Others that might be mentioned are fenelone, menthone, pulegone from pennyroyal, verbenone, and thujone.

While about twenty of those derived from sesquiterpenes have been at least partly studied, the only ones in official oils are santalone and santenone from that of sandalwood.

Aromatic.—Not very many of these have been isolated. Anise ketone is the only one in official oils, being found in those of anise and fennel. Acetophenone and a few derivatives, as well as several quinones, are occasionally present in oils from a limited number of sources.

PHENOLS AND ETHERS

These are quite numerous and are naturally all aromatic. Eugenol, the chief component of oils from clove, pinreta, and bay, is found also in several other official and unofficial oils. Anethole constitutes the greater part of those from anise and fennel, while safrole is the chief ingredient of sassafras, and thymol likewise of thyme. Chavicol, methylchavicol, methyleugenol, npiol, nearone, and thymohydroquinone should also be mentioned.

LACTONES AND OXIDES

Many of these are found in vegetable matter and naturally are also found in the distilled oils. They are of several types as might be expected but are mostly aromatic or alicyclic. Eucalyptol (cineol), which is very widely spread in volatile oils, is the chief compound in many of those from the numerous species of eucalyptus and of others. The official oil of chenopodium contains mainly ascaridol, a peroxide, and one or two derivatives of it. Other lactones and oxides of prominence are coumarin, ergaptol, angelica lactone, sohrerol, and alantolactone. The last, which is obtained from several plants, has been used in the treatment for worms.

ACIDS AND ESTERS

Free acids occasionally constitute a large share of particular oils or may be formed in many by hydrolysis of esters or oxidation of certain compounds. However, we are particularly interested in the acids that are combined with the alcohols already described to form the numerous and usually very fragrant esters. The large majority of flower oils and others that are used for their value in perfumery and as flavors contain as principal ingredients such esters. The acids so combined are aliphatic (saturated or unsaturated), alicyclic, or aromatic. Acetic acid is by far the most common of all, but others of the same class are formic, propionic, butyric, valeric, isovaleric, and others of the series up to stearic acid. Among those of the aromatic group are benzoic, salicylic, anisic, cinnamic, and coumaric. We might also mention angelic, tiglic, geranic, citronellic, santalic, eudesmic, and alantolic acids.

NITROGEN AND SULFUR

More than a score of compounds that contain these elements have been identified, but the particular oils are confined to those from a relatively few species. The rosaceous plants frequently give hydrogen cyanide as an accompaniment of benzaldehyde, as in bitter almond, and alkyl cyanides are sometimes encountered. Methyl anthranilate and its N-methyl derivative are found in citrus oils, while indole and skatole are ingredients of those from some delicate flowers, such as jasmine. Sulfides are prominent in products from asafetida and similar articles, and isothiocyanates or mustard oils come from cruciferous and liliaceous plants.

THE OFFICIAL OILS

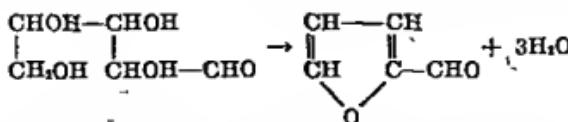
The following table gives a list of the official oils with a few of the ingredients that have been identified in each. To enter all of the compounds that have been found would occupy considerable space and would accomplish no more than emphasize the complexity of composition. In order to demonstrate this partly, numbers are given in parenthesis to indicate approximately how many components have been identified in each oil.

The student is urged to study the official assays for these oils and compare the processes with his knowledge of the chemical properties of the compounds that are determined in each.

REVIEW QUESTIONS

- In what four ways are volatile oils obtained from plants? Which is the usual method?
 - What physical constants are used in examining an oil? What is meant by a sterope?
 - How are each of the following classes determined in oils: acids, esters, alcohols, phenols, ketones and aldehydes, nitrogenous bases?
 - State the chief constituent of each of the following official oils: bergamot, birch-tar, bitter almond, anise, clove, caraway, chenopodium, cinnamon, eucalyptus, fennel, lavender, lemon, myrrh, peppermint, pimento, spearmint, pine-needle, orange, rosemary, sandal, cassiafras, turpentine, thyme
 - Classify the official ways according to class of the chief compounds.
 - How are oils of anise and fennel evaluated? oils of orange and lemon? eucalyptus oil? turpentine oil?
 - Write equations for the assay of volatile oil of mustard, U.S.P. XI.
 - What oils contain n-heptane?
 - Name one compound of each of the classes that have been described and write its formula.

It is obtained industrially by distilling pentosans under pressure with dilute acid.

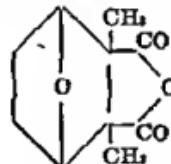


For this purpose any good source of the pentosans may be utilized, such as straw, bran, wood, gums, etc., but oat hulls or corn cobs are the usual materials, because they are otherwise waste and contain much pentosan.

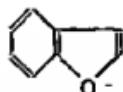
Furfural reacts very much like benzaldehyde in many respects. It reduces silver nitrate about as readily, thereby forming pyromuic acid. With alkalies it gives the Cannizzaro reaction and with potassium cyanide the analogue of benzoin, which is called furoin. With ammonia it gives condensation to produce substances that are like hydrobenzamide. In aqueous solution it yields with phloroglucinol a black precipitate that can be filtered and weighed, a convenient method for quantitative estimation of furfural or pentosans.

The industrial uses are extensive and varied. A large share of the commercial product is employed as solvent for cellulose esters, resins, dyes, and oils, but it is also of value as fungicide, motor fuel, in plastics, and in other ways. The corresponding alcohol and its alphamethyl derivative are found in some volatile oils.

Only a few other compounds containing the furan nucleus are of much importance. The gamma lactones are in this class, but their ring is easily broken. Cantharidin, $\text{C}_{10}\text{H}_{12}\text{O}_4$, the chief constituent of cantharides, is the anhydride of cantharidinic acid, a derivative of furan. Although its exact structure has never been proved by synthesis, the formula given is generally accepted as best expressing its chemical properties.



Finally, a few compounds are known that are derived from coumarone (benzofuran),

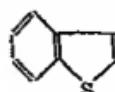


Thiophene occurs in coal tar and is almost a constant impurity (up to 0.6 per cent) in commercial benzene. Its physical properties are remarkably like benzene in many ways; the odor is similar, and its boiling point (85°) and specific gravity are about the same. The chemical behavior is also similar, although it is somewhat more easily affected. Benzene can be freed from thiophene by treating the mixture with sulfuric acid in such a way that only the impurity forms a sulfonic acid. Thiophene can be regenerated from this by treating the lead salt with ammonium chloride. The usual way to remove the thiophene is to treat the impure benzene with mercuric oxide and acetic or stearic acid and to subject the mixture

to distillation. The thiophene forms a mercury compound that does not decompose or distil. Just as do furan and pyrrole, thiophene gives a blue color with isatin and sulfuric acid.

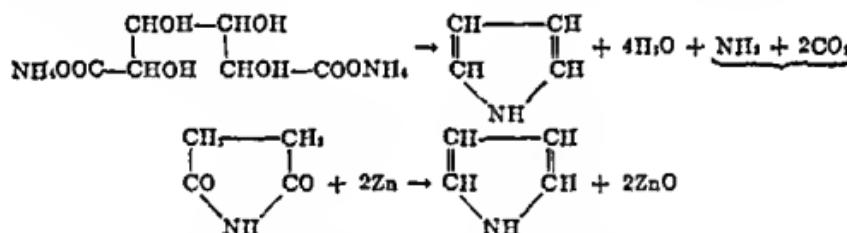
The method of preparation for thiophene is like that used for furan, the beating of a mixture of barium pyromuicate and barium sulfide. The same result can be accomplished by heating sodium succinate or crotonic acid with phosphorus pentasulfide. The dimethyl derivative is formed by heating acetylacetone with the same reagent.

Benzothiophene



and some substitution products are also known.

The most important of the three fundamental compounds is pyrrole, which is found in coal tar and in bone oil. Synthetically it is prepared by heating ammonium mucate with glycerin at 200° or by distilling succinimide with zinc dust.



The dimethyl compound is made by treating acetylacetone with alcoholic ammonia.

Pyrrole is a colorless liquid turning brown in the air, boils at 131°, has an odor like furan, is slightly soluble in water but soluble in acids, and is a weak base. The nitrogenous hydrogen can be replaced in non-aqueous solvents to yield a sodium or potassium salt. With pine wood and hydrochloric acid the vapors give a bright-red color (pyrrole = fiery red). Like furan and thiophene, it gives a blue color with isatin and sulfuric acid. Sodium pyrrole with carbon dioxide forms α -pyrrolecarboxylic acid, a reminder of the Kolbe synthesis. Halogens will substitute for the hydrogen in alpha position but will not add, while nitric acid or sulfuric acid have no action. Iodole or tetraiodopyrrole, C_4I_4NH , a brown powder formed by iodine in alcoholic solution, is used as a substitute for iodoform.

Partial reduction of pyrrole with zinc and acetic acid gives pyrroline



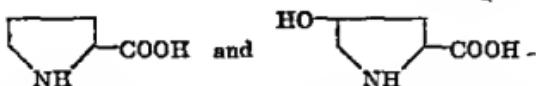
a base strong enough to form stable salts. Further reduction yields pyrrolidine



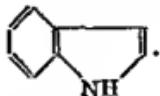
a strong base like the aliphatic substituent part of the molecule in

the nucleus is frequently especially in "

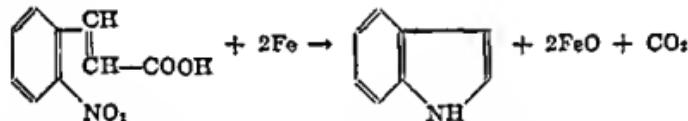
and we will meet it several times again. The amino acids proline and oxyproline, obtained from proteins by hydrolysis, are respectively



The corresponding benzopyrrole fused ring is known as indole,



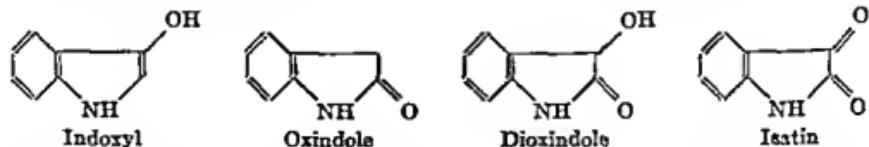
It is a product of putrefactive decomposition of proteins, hence is found as an odorous ingredient of the feces. Skatole, 3-methylindole, has an intensely disagreeable odor and is found also in the feces. Indole is an ingredient of volatile oils from several flowers, including hyacinth, orange, and jasmine. It can be made synthetically in a number of ways, but is usually produced by heating o-nitrocinnamic acid with iron powder and sodium hydroxide.



Both indole and skatole, in spite of their disagreeable odor, are useful perfumes.

Beta-indoleacetic acid is a plant hormone or auxin and is marketed to promote growth of roots. The corresponding derivatives of propionic and butyric acids are also sold for the same purpose.

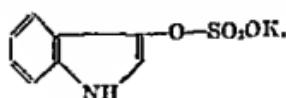
The oxidation of indole furnishes a number of interesting hydroxy substitution products that are usually prepared in other ways. They are indigotin, isatin, dioxindole, oxindole, and indoxyl. Indigotin can be obtained from indole or any of the last three by means of ozone, but nitric acid converts any of them to isatin. On the other hand, progressive reduction of isatin yields dioxindole, oxindole and indole.



As in all primary and secondary amide combinations, $\text{NH}_2-\text{CO}-$ and $\text{RNH}-\text{CO}-$, there can be a tautomerism to $\text{NH}=\text{COH}-$ and $\text{R}-\text{N}=\text{COH}-$. In case of the last three formulas given, the stahle form seems to be the enolic; isatin behaves more as if it were



Indoxyl can be prepared by fusing indigo with potash. Indican, the metabolic detoxication product of indole and found in the urine, is potassium indoxylsulfate,



It is made in the laboratory by warming indoxyl with potassium pyrosulfate.

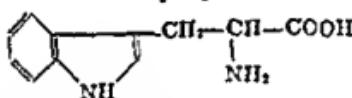
Isatin is an official reagent that gives a blue color when mixed with furan, thiophene, or pyrrole and sulfuric acid.

Indigotin (indigo, indigo blue)



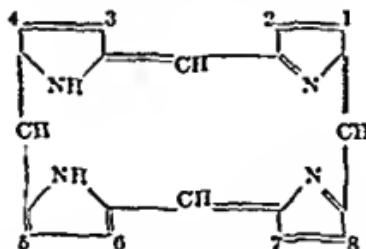
is formed from indole, oxindole, or dioxindole by exposure to air or by action of ozone. It is made commercially by synthetic methods that will be described later. When it is reduced by mild methods, it forms leuco-indigo (indigo white), which is the reverse of indigo. The reverse of indigo disulfonate is indigo carmine.

Tryptophan:



is an important acid from proteins. Its hydroxy derivative has more recently been found also in their hydrolytic products. Abrin, the toxic substance from jequirity seeds, is N-methyltryptophane.

A number of plant and animal pigments contain a common structural pattern of four pyrrole nuclei. The parent compound of these is called porphin.



The simple porphyrins, which are purple pigments found in both the plant and animal kingdoms, are substitution products of this in the eight beta positions. Protoporphyrin, which forms part of the molecule of hemoglobin and which has been synthesized, has four methyl groups (2,4,5,6), two $-\text{CH}_2\text{-CH}_2\text{-COOH}$ groups (6,7), and two vinyl radicals (1,3). These porphyrins form N-metal compounds in which the metallic element is closely associated electronically with all four nitrogen atoms.

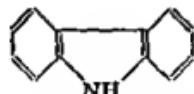
Hemoglobin of blood can easily be split into globin and heme, which contains iron in the ferric state and which can be reduced to heme, containing ferrous iron. If the iron is split out from heme, protoporphyrin

is obtained. Hemin, which contains 1 atom of iron to each molecule, has been synthesized, and its combination with globin, previously obtained from blood, appears to be identical with natural hemoglobin.

Chlorophyll contains magnesium that can be removed in much the same way iron is taken out of hemin. The residual compound contains a hydrogenated porphin pattern of four pyrrole nuclei, although it is not a porphyrin. It has four methyl groups (2,4,6,7), two ethyl (3,5), $-\text{CH}_2-\text{CH}_2-\text{COOphytyl}$ (8), and $=\text{C}(\text{OCH}_3)-\text{OCO}-$ (1).

Bilirubin and biliverdin, the bile pigments, are oxidation products of protoporphyrin. They are not porphyrins although they contain four pyrrole nuclei.

Carbazole



found in coal tar, is used in the manufacture of dyes. It has no basic properties in aqueous solution. It is prepared by heating diphenyl amine to redness.

PYRAZOLE

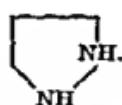
This compound contains 2 nitrogen atoms in the ring,



It has been produced by the action of hydrazine on epichlorhydrin and also of diazomethane on acetylene. Upon partial reduction it is converted to pyrazoline



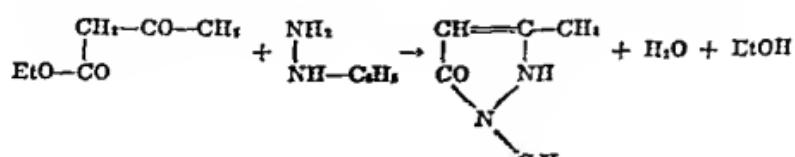
and finally to pyrazolidine



Substitution products of pyrazoline are important drugs, or rather they are related to 5-pyrazolone



1-Phenyl-3-methylpyrazolone is prepared by the action of phenylhydrazine on acetoacetic ester.



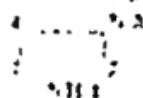
If this is methylated with methyl iodide, it forms 1-phenyl-2,3-dimethyl-pyrazole, which is antipyrine. The same compound would have been obtained if symmetrical methylphenylhydrazine had been used in the reaction with acetoacetic ester. Other pyrazole derivatives could be manufactured by employing various substitution products of the ester and hydrazine.

Antipyrene U.S.P. is a crystalline substance that dissolves readily in alcohol or water. With ferric chloride it gives a red color that turns yellow on the addition of dilute sulfuric acid. With nitric acid it becomes green due to the formation of 4-nitroantipyrene. With tannic acid it yields a flocy white precipitate. It is neutral to litmus but does form salts that are easily hydrolyzed; several of these have been used in medicine.

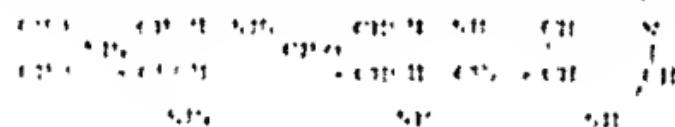
Anteopyrine U.S.P. (Anilopyrine, Pyramidon), 1-phenyl-2,3-dimethyl-4-(4-chlorophenyl)pyrazole, is made by reducing nitroantipyrene and methylating the product. It is not as soluble in water but is alkaline to litmus and can form stable salts. Ferric chloride produces with it a blue color that changes to violet-red with acid, a reaction distinguishing from antipyrene. Anteopyrine has been known to cause granulocytopenia, and caution should be advised in its use.

Pentacrylate, an official reagent, is 1-pentaacetyl-3-methyl-4-nitro-5-hydrazinopyrazole.

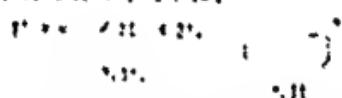
It reacts with pyrrolidine in imitation of glutamine:



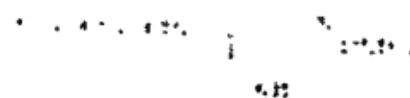
stable to the action of glycolaldehyde, ammonia, and formaldehyde.



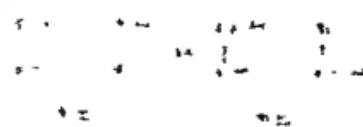
It reacts with pentaacetylacetone as follows:



Each of the above products is soluble. If these heated, it becomes decomposed and converted to pentacetyl acetone, a very potent reagent that is probably partly responsible for several reported cases of tetrahydroantipyrene. It can be destroyed U.S.P.



The reaction of the latter substance is as follows. It reacts with one mole of acetyl chloride to form the corresponding pentaacetyl derivative of Pentacrylate:



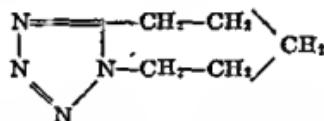
in the enol form, is 2,4-dihydroxyimidazole. It is obtained by reaction of glycollic acid and urea. Diphenylhydantoin Sodium U.S.P. (Dilantin Sodium), the salt of 5,5-diphenylhydantoin, is used in epilepsy. Other closely allied compounds are allantoin (5-carbamylaminohydantoin) which has been used in medicine, and parabanic acid (5-ketohydantoin or oxalylurea).

Triphal N.N.R. is a gold compound derived from benzoimidazole.

Triazole and tetrazole

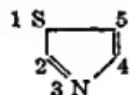


are also known. The latter is represented in medicine by Metrazol N.N.R. (Pentamethylenetetrazole)

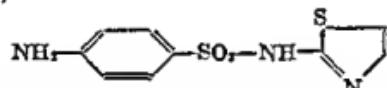


which is used like camphor and to subject schizophrenic patients to shock. Cyclohexylethyltriazole has more recently been suggested for the same purpose.

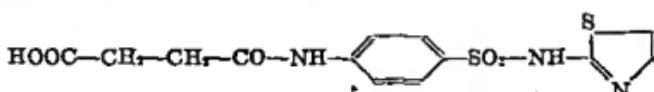
Thiazole is the parent of several useful compounds.



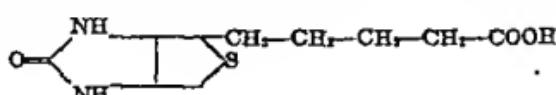
Sulfathiazole U.S.P.,



made by the reaction of sulfanilyl chloride and 2-aminothiazole, and Sulfathiazole Sodium U.S.P. are important new additions to the list of sulfa drugs. Another is Succinylsulfathiazole U.S.P. (Sulfasuxidine),



Biotin, which has been called the supervitamin and which is apparently essential to the life of yeast and other plants, perhaps also of man and other animals, has recently been synthesized. It is a derivative of condensed thiazole and imidazole nuclei,



REVIEW QUESTIONS

1. Write the formulas of furan, thiophene, and pyrrole and all of the monomethyl substitution products of each and name them.
2. How are furan, thiophene, and pyrrole made from mucic acid? Write equations.

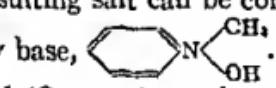
3. How does each behave with hydroxyl and chlorine and?
4. How is *tert*-butyl carbamate synthesized? Write equation. What acid is formed in synthesis?
5. How does each behave with sulfuric acid? Write the equation.
6. Where does the reaction occur? How is it separated from benzene? Why is this necessary?
7. How does pyridine compare with benzene in chemical properties? What is formed in incomplete reduction?
8. How is it prepared? Write the equation. What is its stability?
9. What are its uses and derivatives?
10. Write four facts about alkyl boranes, our three, obtained by, borane, boron, and boron hydride.
11. What are some advantages of boron hydrides, try to relate.
12. What is the characteristic pattern of the polyhydride? What is the relation of boron hydride and alkyl borane to these?
13. Write formulae of pyrazine, pyrazole, imidazole, piperazine, piperidinone, and.
14. Write equations for the preparation of phenylmethylhydrazine. How is anti-pyriphenone formed?
15. Give the formulas of imidazole, piperidine, piperazine, hydrazine, and diazepam.
16. What is meant by their *let them let me*?

CHAPTER XXXVII

HETEROCYCLIC-SIX MEMBER

PYRIDINE

PYRIDINE is derived by replacing one CH group of benzene by an atom of nitrogen,  N. It occurs in coal tar, the usual source, also in bone oil and in the products of distillation of many organic materials. It is formed by heating any of its carboxylic acids, such as nicotinic acid. Various derivatives can be made from aliphatic compounds in a number of ways involving ring closure.

Pyridine is a mobile liquid with a characteristic odor, a specific gravity almost the same as water, with which it is miscible. The boiling point is 115°, but mixtures with water are difficult to separate by distillation. It is an extremely stable substance under most conditions, since boiling nitric acid, chromic acid, or permanganate have no effect, and halogens or sulfuric acid will cause substitution with great difficulty. Nascent hydrogen in alcohol or hydrogen with platinum in acetic acid will give piperidine,  NH, by addition of 6 hydrogen atoms, while in water the products are glutardialdehyde and ammonia. Hydrogen iodide at 350° yields pentane and ammonia. Pyridine is a very weak base, dissociation constant 2×10^{-7} , and will not affect litmus, although methyl orange is changed to yellow. Its aqueous solution precipitates the hydroxides of iron, chromium, and aluminum. Methyl iodide will add as usual, and the resulting salt can be converted by silver oxide to the very strong quaternary base,  . The salt formed by adding cetyl chloride is marketed (Ceepryn) as a bacteriostatic.

The three possible methyl derivatives, called picolines, are found in coal tar. They oxidize readily to the corresponding acids, which is quite important for making β -pyridinecarboxylic (nicotinic) acid. The necessary β -picoline for this reaction may be obtained by heating lime with acrolein and ammonia or with strychnine. The six possible dimethylpyridines, called lutidines, and the six possible trimethylpyridines, known as collidines, occur in coal tar and bone oil. In each case all alkyl groups can be oxidized easily to carboxyls.

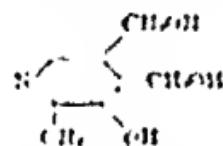
The three carboxylic acids of pyridine are amphoteric, although the basic properties are very weak. The alpha compound, picolinic acid, is obtained by oxidizing α -picoline with potassium permanganate. It is a crystalline substance melting at 137°. Isonicotinic acid, the gamma compound, melts at 317°, one of the few organic compounds that have such a high melting point without decomposing.

Nicotinic Acid U.S.P. (β -pyridinecarboxylic acid) consists of colorless crystals melting at 234° to 236°. It decomposes easily when heated with lime to form pyridine. It cannot be extracted with ether, in which it is

insoluble, but can be purified by recrystallization from water, because it is freely soluble hot but sparingly cold. It forms an insoluble, blue copper salt. The acid can be prepared from β -picoline by oxidation or from nicotine which gives its name. Nicotinamide U.S.P. is used in medicine for the same purpose. Nikethamide N.N.R., its diethyl derivative, has been employed for a number of years as a stimulant under the title of Ceratine; it is marketed in 25 per cent aqueous solution.

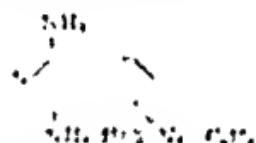
All six of the dicarboxylic acids are known, but only two are of particular interest to us. Quinilic acid (2,3) can be obtained by oxidizing quinoline with potassium permanganate. Like succinic acid, of which it is a derivative, it forms an anhydride, but at 190° loses carbon dioxide to become 1,1-dihydroxy-2,3-dihydro-1,2-dihydro-4H-pyridine-4,5-dicarboxylic acid. Cinchonemonic acid (3,4) is formed by the action of nitric acid on quinine or of permanganate on isoquinoline. When heated it loses carbon dioxide and produces ironocinquinic acid. The oxidation of leptoline gives leptoceric acid, a pyridinecarboxylic acid.

Pyridoxine Hydrochloride N.N.R. (Adermin), the so-called Vitamin B₆, is found in yeast, liver, corn, or rice-bran. First isolated in 1937 and synthesized in 1942, it is 3-hydroxy-2-methyl-1,4-dihydroxymethylpyridine.

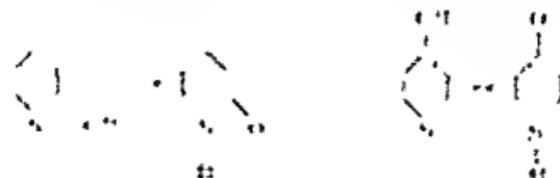


Fatty acids U.S.P. (oleic acid, linoleic acid), $\text{NH}_2-\text{C}_6\text{H}_4-\text{SO}_2-\text{NH}-$
C₆H₄N₃, and fatty acids Potassium U.S.P. are important salts drugs.

Diphenylmethylacetate is a potent urinary antiseptic, in 3-phenylacetanilide, $\text{C}_9\text{H}_{10}\text{NO}_2$, m.p. 104°, with the formula

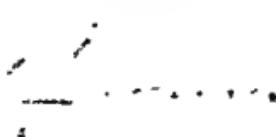


The following derivatives of pyridine are very protective substances. The 2,6-dimethyl compound resists the leaching out by migration of the methyl groups to the para position.

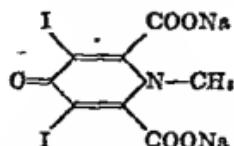


The history of classical speech treatment

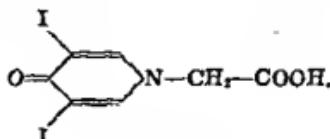
Consequently, the information available on the quality of the data is limited.



obviously an alphapyridone. Neo-Iopax N.N.R. is the disodium salt of 3,5-diiodochelidamic acid or N-methyl-3,5-diido-4-pyridone-2,6-dicarboxylate

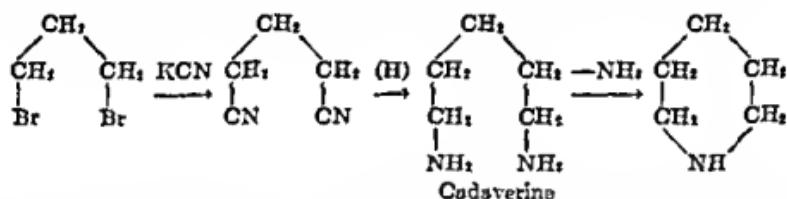


Chelidamic acid is N-methyl-4-pyridone-2,6-dicarboxylic acid. Diodrast N.N.R. is a mixture or loose combination of diethanolamine and 3,5-diido-4-pyridone-N-acetic acid,



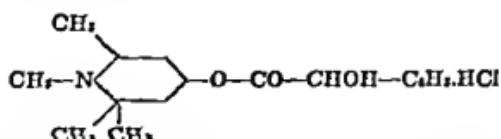
PIPERIDINE

The complete reduction of pyridine by nascent hydrogen in alcohol, or by hydrogen and platinum black in acetic acid, gives piperidine,  NH. It occurs in pepper combined with piperic acid as piperine and can be obtained from the latter by hydrolysis. Synthetically it is produced from cadaverine, $\text{NH}_2-(\text{CH}_2)_5-\text{NH}_2$, by loss of ammonia or through the following series of reactions from trimethylene bromide:



Piperidine is a mobile liquid that has an unpleasant odor, is miscible with water, and boils at 106° . It is a strong enough base to affect litmus and is comparable to aliphatic secondary amines. It can be reconverted to pyridine by heating with sulfuric acid at 300° . Since each carbon has 2 hydrogens, piperidine can form many more substitution products than pyridine, and the nitrogenous hydrogen can also be replaced by alkylation, by acylation, or by a nitroso group.

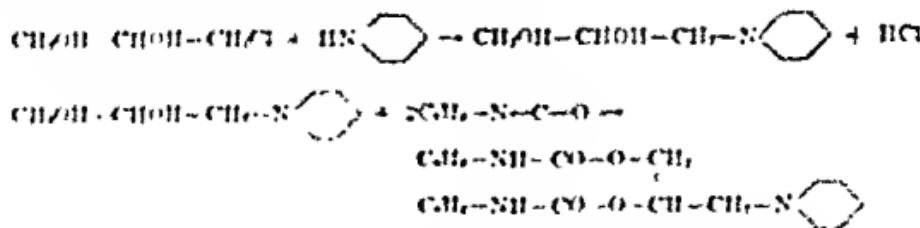
Eucatropine Hydrochloride U.S.P. (Euphthalmine), the salt of 1,2,2,6-tetramethyl-4-mandeloxy piperidine



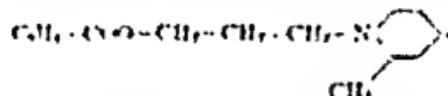
is used as a mydriatic in place of atropine or bomatropine.

Diothane Hydrochloride N.N.R. (Diothane), piperidinopropane-diiodophenylurethane hydrochloride, is used as substitute for cocaine and pro-

caine. It is manufactured by combining piperidine and glycerol monochlorhydrin in the presence of an alkali and treating the product, which is twice an alcohol, with phenyl isocyanate.



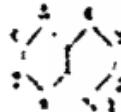
Mesocaine N.N.R. is another local anesthetic of the type of procaine, and is racemic although containing an asymmetric carbon atom. It is the hydrochloride of α -(2-methylpiperidino)-propyl benzoate.



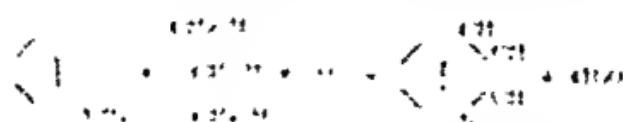
Demecol, more recently introduced as analgesic and spasmolytic, is ethyl N-ethyl-4-phenylpiperidine-1-carboxylate.

QUINOLINE

Quinoline is related to pyridine in the same way that naphthalene is related to benzene. From pyridine alone it is derived by replacing an alpha CH by nitrogen, giving



It is a colorless solid benzene, and can be obtained by heating quinoline with a base. However, in most cases it is made from aniline and phthalic anhydride (Benzene-1,2-dione), that can also be employed in making many other quinoline derivatives. A mixture of the two is heated with CuCl_2 and sulfuric acid to give piperidines substituted with a quinoline.



In this reaction anisole is a by-product formed and added to the product. Mesocaine and its salts are prepared in the following way from aniline:

Quinoline and about 3 g. of potassium iodide with a few drops of concentrated glacial acetic acid are heated to 100° C. for 10 minutes, and the temperature is then raised to 120° C. for 10 minutes. The excess of iodine is removed by the addition of dilute sodium thiosulfate. It is then cooled, filtered off from the solid residue, and the filtrate is concentrated. The residue is dissolved in ether, and the ether solution is washed with dilute sulfuric acid. After the ether has been dried and the ether removed, the residue is purified by recrystallization from ether. Mesocaine is a white crystalline product, m.p. 104° C., soluble in alcohol, ether, and chloroform, and insoluble in water.

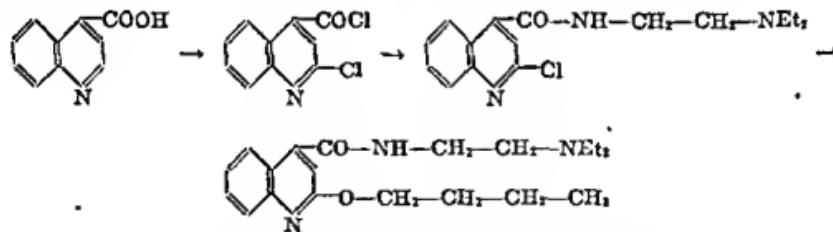
generally involves less direct methods. Oxidation gives quinolinic acid, a derivative of pyridine, showing that the benzene ring is attacked first. On the other hand, reduction affects the pyridine part to give dibydro, and tetrahydro compounds.

Cinchophen N.F. (Phenylcinchoninic Acid), 2-phenylquinoline-4-carboxylic acid, was introduced into medicine as Atophan, and has since been found to be an insidiously dangerous drug. Its hydrochloride is sometimes employed as Chloroxyl, while the allyl (Atoquinol) and other esters have also been recommended.

Neocinchophen U.S.P. (Novatophan, Tolysin) has largely replaced the dangerous cinchophen, although it also must be used cautiously. It is 6-methyl-2-phenylquinoline-4-carboxylic ethyl ester, so it differs from cinchophen in having a methyl group and in being an ester. Neither compound is soluble in water, but cinchophen is soluble in bases and can be reprecipitated on acidifying.

Chiniofon Powder U.S.P. is a mixture of 8-hydroxy-7-iodoquinoline-5-sulfonic acid with sodium carbonate and contains some of the sodium salt. There is still some uncombined acid, because moistening the powder with water leads to liberation of carbon dioxide. The aqueous solution gives an emerald-green color with ferric chloride, attributable to the phenolic group. **Vioform N.N.R.**, described as 5-chloro-8-hydroxy-7-iodoquinoline was originally introduced as a substitute for iodoform. **Diodoquin N.N.R.**, 5,7-diido-8-hydroxyquinoline, is similar.

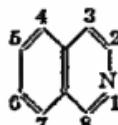
Nupercaine N.N.R. (Percaine), a local anesthetic of the procaine type, is made from cinchoninic acid, quinoline-4-carboxylic acid, obtainable from cinchonine by oxidation. This is converted by chlorination to α -chlorocinchonyll chloride, which is combined with unsymmetrical diethylethlenediamine, $\text{NH}_2\text{---CH}_2\text{---CH}_2\text{---NET}_2$, and then heated with sodium n-butylate.



It is finally converted to the hydrochloride, which is nupercaine.

Pamaquine Naphthoate U.S.P., the methylene-his- β -hydroxynaphthoate of 8-(4-diethylamino-1-methylbutylamino)-6-methoxyquinoline, was originally introduced as antimalarial under the title of Plasmochin.

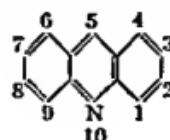
Isoquinoline.—This compound, also found in coal tar, is derived from naphthalene by replacing a heta CH by nitrogen.



It melts at 23° and boils at about 243°. The constitution follows from its synthesis using the imide of o-carboxyphenylacetic acid, and from the

fact that it oxidizes to cinchomeronic and phthalic acids. The nucleus of isoquinoline is found in some of the alkaloids, where we will meet it again.

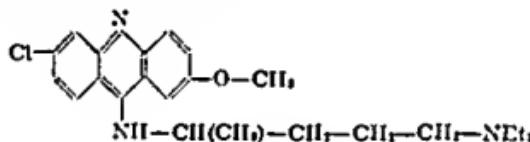
Acridine.—Another nitrogenous base found in coal tar is acridine, which is derived from anthracene by substituting nitrogen for CH in the middle ring.



An older system of numbering started with 1 at the position given here as 4 and proceeded clockwise. Acridine is a colorless solid that melts at 110° and is insoluble in water. It is a weak base and dissolves in acids with a greenish fluorescence. It can be synthesized by heating diphenylamine with formic acid and zinc chloride.

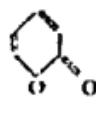
Acriflavine N.F. (Acriflaviac Base), 2,8-diamino-N-methylacridinium chloride, mixed with some of the unmethylated compound, is soluble in water. **Acriflavine Hydrochloride N.F.** (Trypaflavinae) is also soluble in water and used in the same way. **Proflavine N.N.R.** is the acid sulfate of 2,8-diaminoacridine.

Quinacrine Hydrochloride U.S.P. (Atabrine, Mepacrine Hydrochloride) has recently been manufactured in large quantities for antimalarial treatment. It is the salt of 8-chloro-3-methoxy-5-(4-diethylamino-1-methylbutylamino)-acridine.

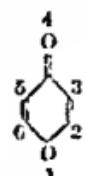


PYRONES AND PYRYLIUM SALTS

Since oxygen has a valence of 2, it cannot replace nitrogen in pyridine, quinoline, isoquinoline, or acridine. Any compounds containing oxygen in a six-membered ring should, therefore, lack the resonance and stability of aromatic compounds. The simplest representatives of these are the pyrones, which correspond to the pyridones, alpha and gamma.



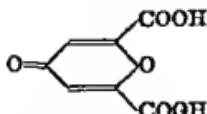
α -pyrone



γ -pyrone

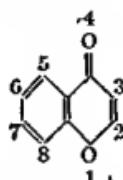
It will be noted that α -pyrone and any substitution products are δ -lactones of unsaturated acids, and other lactones, of course, can also be considered heterocyclic. Their rings are easily opened, so we can dismiss them from further consideration at this point. When α -pyrone is heated with ammonia, it is transformed to α -pyridone.

Two derivatives of γ -pyrone are found in nature associated with alkaloids. Chelidonic acid

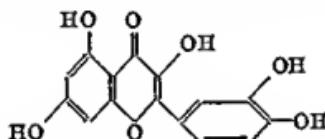


occurs in *Chelidonium majus* together with several alkaloids, including chelidonicine. Meconic acid, occurring in opium with its numerous alkaloids, is 3-hydroxychelidonic acid.

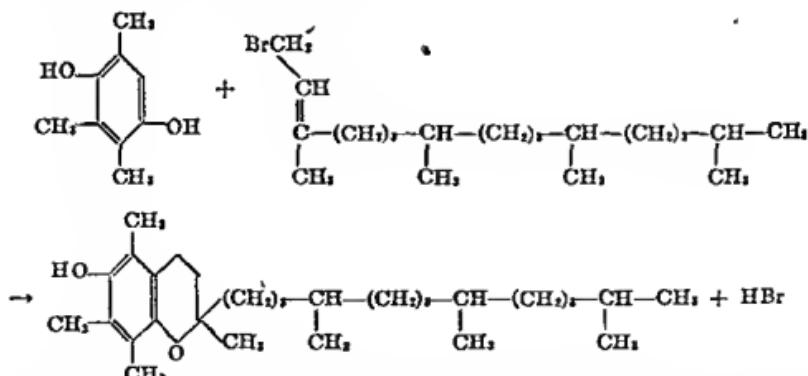
Some of the plant pigments are substitution products of chromone, a combination of pyrone and a benzene ring,



The flavonols, yellow pigments of plants, are hydroxy derivatives of 2-phenylchromone (flavone). They include chrysins, luteolin, quercetin, and rhamnetin. As example, quercetin has the formula

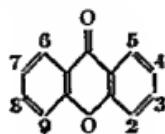


Vitamin E or α -tocopherol, $C_{29}H_{50}O_2$, was synthesized in 1938 from phytol bromide and 2,3,6-trimethylquinol.

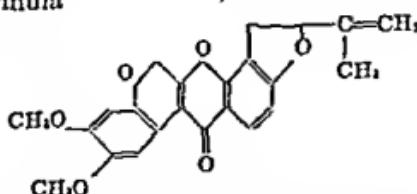


It is an insoluble, yellow, odorless oil that can be converted to crystalline esters for identification. β -Tocopherol and γ -tocopherol, which occur with the alpha form in nature, differ in structure by one methyl group and are much less active physiologically.

Gentisin, occurring in gentian, is 5,7-dihydroxy-3-methoxyxanthone. Xanthone is

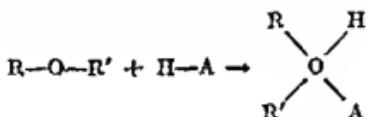


Rotenone, found in cube, derris, and other plants, is a more complicated compound of the formula

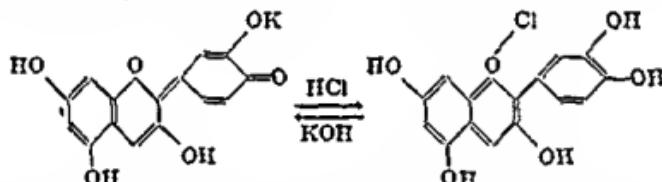


Brasilin of brazil wood and hematoxylin and hematein of logwood are similar; the last are official reagents.

Under some circumstances oxygen has an apparent valence of 4, just as it does when ethers add substances like acids.

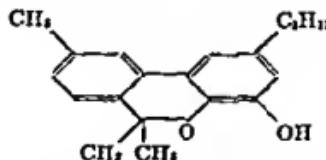


When O substitutes for CH₂ in a cyclohexane nucleus, making an inner ether, such a compound may add substances in the same way, with acids to form pyrylium salts. These are only known in compounds that contain other substituents. They are best illustrated by the anthocyanidins, the blue colors of plants. The most common of these is blue-violet cyanidin, whose chloride is red. The change that occurs in passing from the potassium salt to the pyrylium salt is



Pelargonidin and delphinidin are similar blue pigments that differ only in the number of hydroxyl groups. All three compounds are combined in plants as glycosides, the anthocyanins.

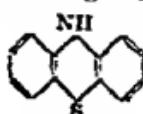
Cannabinol, the active constituent of cannabis, is presumed to have the formula C₂₁H₃₀O₂, and it is suggested that its structure is



Picrotoxin U.S.P., C₁₅H₁₄O₁₁, obtained from fish berries, is not a glycoside although sometimes described as such. By cleavage it is converted to picrotoxinin, C₁₅H₁₄O₆, and inactive picrotin, C₁₅H₁₄O₇, which are related to cannabinol.

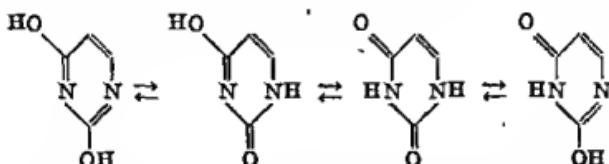
Phenanthroline, an official reagent, is derived from phenanthrene by putting nitrogen atoms for CH at positions 4 and 5.

Phenothiazine is prepared by heating diphenylamine with sulfur. It



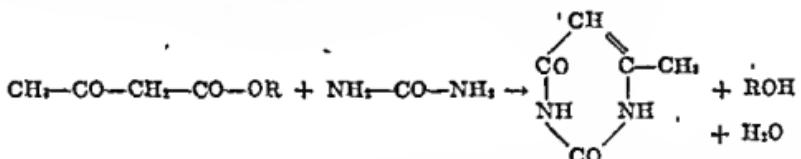
and guanine. The last two are of the so-called purine class, which will be taken up shortly.

Uracil, 2,6-dihydroxypyrimidine, is analogous to resorcinol. Like all such compounds that have the grouping $\text{—COH}=\text{N}$ or $\text{—COH}=\text{CH}$, this shows ketone-enol tautomerism.



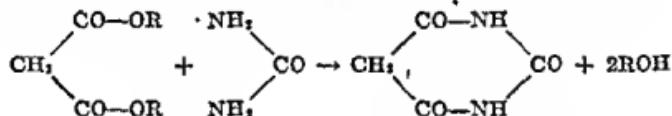
In the enol form the hydroxyl hydrogen is replaceable by a metal, so that the compounds may be either acid or base. In cyclic compounds this tautomerism is particularly pronounced, and hydroxy derivatives of pyrimidine are often at least as acidic as acetic acid.

4-Methyluracil can be made by the action of acetoacetic ester and urea.

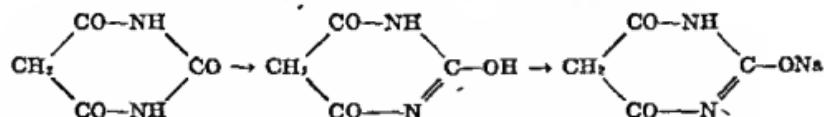


Cytosine, 2-hydroxy-6-aminopyrimidine, and thymine, 2,6-dihydroxy-5-methylpyrimidine or 5-methyluracil, also show the ketone-enol tautomerism.

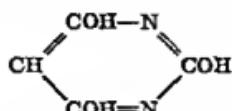
Barbituric acid, 2,4,6-trihydroxypyrimidine, is usually referred to as malonylurea and is made by beating malonic ester with urea.



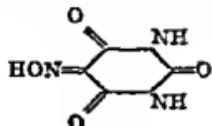
Because of enol formation, it is about as acidic as acetic acid.



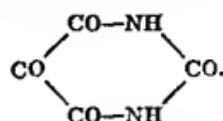
The complete enol formula shows its relation to pyrimidine.



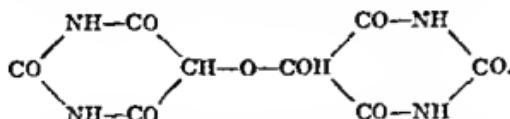
The methylene (5) hydrogens, being between two carbonyls, are reactive toward halogens, oxidation, etc., just as is the case in ester. The dihydro compound easily parts with its bromine to : antiseptic and is assayed by liberation of iodine from iodide in the : acid. Nitrous acid reacts on the hydrogen to give : acid,



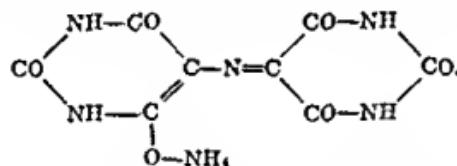
known as violuric acid. This reduces to the amino compound, uramil, important in the synthesis of uric acid. Dialuric acid, 5-hydroxybarbituric, is strongly dibasic. Oxidation of barbituric, uric, or dialuric acid gives alloxan or mesoxalylurea,



When this is combined with dialuric acid, addition takes place to form alloxanthine,



Heating with ammonia converts this to ammonium purpurate or murexide, the purple color formed in the tests for caffeine, uric acid, and other purines,



The most important compounds belonging in this class are the so-called barbitals, derived by replacing hydrogen of barbituric acid by hydrocarbon and other radicals. Since these were discovered in 1903, several hundred of them have been made, and a few are very often used in medicine as hypnotics and anesthetics. The substitution could be for the two hydrogens (1 and 3) that are connected to nitrogen, but in most of the substances now used the radicals are in position 5. Those compounds with but a single radical in this position are physiologically inactive, so all of the marketed articles have two substitutions, both in the methylene group.

The manufacture of each follows the process given for the parent compound, using substituted malonic ester. The student will remember that two radicals could be introduced, one at a time, into malonic ester by successive treatment with sodium in alcohol and with an alkyl halide. Presuming that two have thus been put into the ester, urea is added and the mixture is heated. The product is not soluble in cold water but dissolves in hot water, so it is recrystallized from this medium. It can also be purified by extraction with ether or by dissolving in alkali and reprecipitating with acid. All of them are decomposed by boiling with solutions of sodium carbonate or hydroxide.

Barbital U.S.P. (Diethylbarbituric Acid, Barbitone, Diethylmalonylurea), the first one used and still very popular, was introduced under the name of veronal. Barbital Sodium U.S.P., originally called medinal, is a sodium salt that has the advantage of being usable in liquid preparations. Naturally it is incompatible with acids or with substances that have an acid reaction.

Phenobarbital U.S.P. (Phenylethylbarbituric Acid) was introduced under the title of luminal at the same time as veronal. Its sodium salt is Phenobarbital Sodium U.S.P.

Pentobarbital Sodium U.S.P. is the sodium salt of pentobarbital (nembutal) which has an ethyl and the radical of methylpropylcarbinol.

The others described in New and Nonofficial Remedies are listed in tabular form. It will be noted that the total number of carbon atoms in the two radicals is from 4 to 8. Some have attempted without much success to correlate such numbers, the amount of branching, toxicity, duration of action, and other factors. Even the old theory that ethyl groups are superior to methyl in narcosis cannot be uniformly maintained. There are undoubtedly differences in physiological action between the various barbitals, but this is hardly the place to open such a discussion.

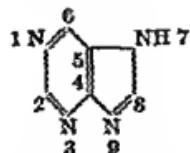
Name	<i>R</i> ₁	<i>R</i> ₂	Melting point
Barbital	Ethyl	Ethyl	190
Ipral	Ethyl	Isopropyl	203
Neonal	Ethyl	n-Butyl	127
Amytal	Ethyl	Isoamyl	155
Pentobarbital	Ethyl	Pr—CH—CH ₃	130
		↓	
Oxtal	Ethyl	n-Hexyl	125
Phenobarbital	Ethyl	Phenyl	177
Phanodorn	Ethyl	Cyclohexenyl	174
Dial	Allyl	Allyl	173
Sandoptal	Allyl	Isobutyl	139
Alurate	Allyl	Isopropyl	141
Seconal	Allyl	Pr—CH—CH ₃	100
		↓	
Pernoston	β-Bromallyl	sec-Butyl	133
Nostal	β-Bromallyl	Isopropyl	179
Evipal	Methyl	Cyclohexenyl	145
Pentothal	Ethyl	Pr—CH—CH ₃	159

Some of those listed are used chiefly or entirely in the form of sodium or calcium salts. It will be noted that pentothal and pentobarbital are described with the same radicals, but the former is made from thiourea and contains one sulfur atom in place of oxygen.

Sulfadiazine U.S.P. (2-sulfanilaminopyrimidine) and Sulfadiazine Sodium U.S.P. are important compounds of the sulfa group. Sulfamerazine N.N.R. (4-methyl-2-sulfanilaminopyrimidine) and Sulfamerazine Sodium N.N.R. are more recent.

PURINES

Quite a large number of natural and artificial compounds are derivatives of purine, C₁₀H₁₄N₄, a compound composed by condensing the nuclei of pyrimidine and urea,



This substance itself can be prepared from uric acid, but it is of no practical importance.

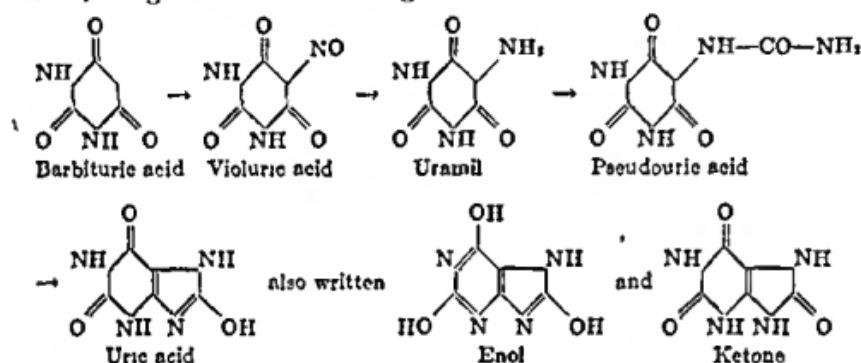
Adenine, 6-aminopurine, is obtained from nucleic acids by hydrolysis, also guanine, 2-amino-6-hydroxypurine. The pentose (d-ribose) molecule is attached at 9 to give a substance that is called a nucleoside; with adenine it is known as adenosine. The phosphoric acid is linked to the pentose,

and the combination of purine, pentose, and phosphoric acid is termed a nucleotide. Pentnucleotide N.N.R. is a mixture of such substances.

Hypoxanthine, a normal degradation product of certain proteins and probably obtained directly from adenine by deamination, is 6-hydroxypurine. It is accompanied by xanthine, 2,6-dihydroxypurine, an official reagent, which can be obtained in the same way from guanine.

Uric acid, 2,6,8-trihydroxypurine, is a normal but variable excretion product during metabolism and is sometimes deposited in the form of its insoluble sodium acid salt in calculi and in the joints. It is also found in the excrement from certain birds and serpents. It is an insoluble, crystalline substance that is a weak dibasic acid and, hence, forms normal and acid salts. It is described as an official reagent.

The steps in the synthesis of uric acid, started more than one hundred years ago by Liebig and Wöhler and finally completed in 1897 by Emil Fischer, are given in the following outline.



Caffeine, theobromine, and theophylline are N-methyl derivatives of xanthine. In the ketone formula of the latter there are three hydrogens at 1, 3, and 7 capable of being replaced. If both 1 and 3 are occupied, there is no longer the possibility of reverting to the enol formula, but the third hydrogen is capable of reacting with bases. However, if all three are displaced by alkyl, the substance is no longer an acid.

Caffeine U.S.P. (Theine) is 1,3,7-trimethylxanthine or 2,6-dihydroxy-1,3,7-trimethylpurine. It is usually prepared from tea, which contains about 3 per cent, but is also found in coffee (about 1 per cent), guarana, and cocoa, and can be made synthetically. In respect to amount sold among so-called alkaloids, it is second only to quinine; about 750,000 pounds are marketed annually.

Caffeine is neutral to litmus and does not form metallic salts. As a base it is very weak but will form unstable salts with acids. When evaporated with a mixture of potassium chlorate and hydrochloric acid and then exposed to the vapors of ammonia, it forms the purple color of murexide (ammonium purpurate). Other purine derivatives like uric acid and theobromine also give this test. It can be administered as Citrated Caffeine U.S.P., Caffeine with Sodium Benzoate U.S.P., or Caffeine with Sodium Salicylate N.F.

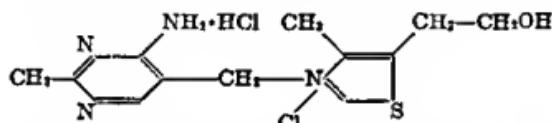
Theophylline U.S.P. (Theocin), 1,3-dimethylxanthine, is found in tea. It is sparingly soluble in water but dissolves readily in alkalies to form a salt. By methylation it can be converted to caffeine, as can be done in the assay. Theophylline with Ethylene Diamine U.S.P. is an unstable com-

hination of acid and base; even carbon dioxide will precipitate the theophylline. Theophylline with Sodium Acetate U.S.P. is another soluble combination.

Theohromine, 3,7-dimethylxanthine, is found in cocoa and kola. Like theophylline it is sparingly soluble but dissolves in alkali, and it is easily converted to caffeine by methylation. Several mixtures with sodium salts are employed in medicine to get a soluble preparation. The most popular of these are Theobromine with Sodium Salicylate U.S.P. and Theocalcin N.N.R.

THIAMINE

The original vitamin B was discovered in 1911 and named "vitamine." At that time B_1 was probably isolated in a very crude state and naturally was given an erroneous formula. Not until many years later was its structure determined and its synthesis accomplished. The compound was then given the name thiamine and marketed as the hydrochloride.

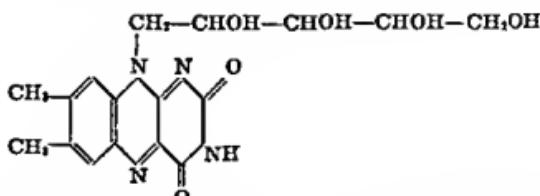


It is seen to be a quaternary salt, a combination through methylene of 4-amino-2-methylpyrimidine and 4-methyl-5- β -hydroxyethylthiazole chloride.

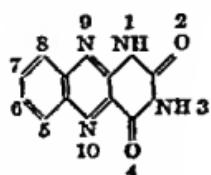
Thiamine Hydrochloride U.S.P. (Vitamin B_1 Hydrochloride) forms white crystals that are very soluble in water, and are acid to litmus. The fluorescence test with potassium ferricyanide is characteristic. The pyrophosphoric ester of thiamine is the enzyme, cocarboxylase.

RIBOFLAVIN

From the original vitamin B has been separated B_1 or thiamine, B_2 which has also been called G and later riboflavin, and several other factors. B_2 was later found to be identical with a natural lactoflavin, whose molecule was soon shown to contain a modified d-ribose. The name was, therefore, changed to riboflavin, and the structure was demonstrated by synthesis.



The synthesis was made from dimethylphenylenediamine, using d-ribose and alloxan. Its structure is usually referred to alloxazine, first prepared in 1891.



A combination of riboflavin with phosphoric acid and protein is known as a yellow enzyme.

REVIEW QUESTIONS

1. Write formulas of pyridazine, pyrazine, and pyrimidine and number the atoms of the latter.
2. Show why hydroxyl derivatives of pyrimidine are acid and how the formulas are written in two forms.
3. How is barbituric acid made? Write equation.
4. Write the formulas of sulfadiazine, sulfapyrazine, sulfamerazine, and each of their sodium salts.
5. Write equations for the preparation of a barbital from malonic ester.
6. Name the official barbitals and give their formulas. Name six others commonly used.
7. Why are the barbital salts incompatible with acids?
8. Write formulas of purine, hypoxanthine, xanthine, uric acid, caffeine, theophylline, and theochromine.
9. How can theophylline be converted to caffeine? Why is caffeine not acid?
10. Describe the murexide test for purine derivatives.
11. Outline the method used to synthesize uric acid. Write its ketone and enol formulas.
12. Write the formulas of thiamine hydrochloride and riboflavin.

CHAPTER XXXIX

ALKALOIDS

Although this group of compounds is probably the most important of all to medicine, yet we must admit at the outset that it is impossible to set definite limits on what substances shall be included. The alkaloids (=like alkalies) were originally defined as nitrogenous plant bases, but later this was limited to potent ones in order to exclude proteins and amino acids. Today, however, hundreds of them are synthetic and some are obtained from animals. Furthermore, slight changes in the molecule often give a product that is not physiologically active, yet chemically it is certainly closely related to the original potent compound. Even the official descriptions are not consistent, because some substances of the Pharmacopœia that are surely classed as alkaloids are not called so; *e. g.*, scopolamine. The Formulary is equally at fault; *e. g.*, brucine. Again, if ephedrine is an alkaloid, why should not epinephrine be one also? Some prefer to say that they should be limited to derivatives of pyridine, quinoline, or isoquinoline, but important substances like pilocarpine and histamine would then be excluded. One can only conclude that it is impossible to set any limits; we will simply call them nitrogenous bases.

Having set no definite restrictions on the class, we could hardly expect any general statements on names and structure, yet a few observations can be made. They mostly have a single atom of nitrogen, although some, like ergotoxine have up to 5, and this nitrogen is most often tertiary, sometimes secondary and even primary. The names all end in -ine according to established chemical rules; the Pharmacopœia follows this custom, but some members of the medical profession prefer to leave off the final *e*. Those that contain no oxygen are frequently liquids, but when oxygen is a constituent the substance is a solid.

The physical properties of so heterogeneous a group are surprisingly uniform. Practically all of the common compounds are solids, the exceptions being coniine, nicotine, and sparteine. Some, like eserine, are so hygroscopic that they are usually obtained as thick liquids. Almost without exception they are bitter in taste, although they may vary in degree up to strychnine, which is reputed to be the most bitter of all substances. The alkaloids are generally insoluble in water or very sparingly soluble; some of the liquid ones furnish an exception, since they are miscible. They are all soluble in alcohol, ether, chloroform, and other organic solvents, although we will meet some important alkaloids that do not behave this way. The strength of their reaction varies up to those that will reddens phenolphthalein, some being so weak that their salts are not stable in water.

The alkaloidal salts with common acids are generally soluble in water and alcohol but insoluble in organic media. This statement cannot be accepted unconditionally, because important compounds like quinine sulfate are insoluble in water, and a number of salts are notably soluble in chloroform. The alkaloids, like other amines, form numerous double salts,

especially with mercury, platiaum, and gold, and many of these are obtained as precipitates.

A number of so-called alkaloidal precipitants are used in a general way for the purpose of isolation and identification, usually in an acid solution of the salt. They are not uniformly reliable, but may be of considerable aid if we do not confine ourselves to a single reagent. The following list gives the composition of those that are most often employed.

- Iodine and potassium iodide (Wagner's reagent)
- Potassium cadmium iodide (Marme's reagent)
- Mercuric chloride
- Gold chloride
- Phosphotungstic acid (Scheihler's reagent)
- Phosphomolybdic acid (Soanenschein's reagent)
- Platium chloride
- Potassium dichromate
- Silicotungstic acid

In the identification of bases in toxicology, drug analysis, and phytochemistry, hundreds of reagents are employed. In the majority of cases the method is purely empirical and depends on a color as the deciding factor. No attempt will be made here to list these substances or describe the processes in which they are used. A large share of the reagents are oxidizers or reducers, but a few dehydrate or act in a special way. Among them might be mentioned as illustrations sulfuric acid, nitric acid, molybdic oxide, formaldehyde, ferrie chloride, selenous acid, and iodic acid.

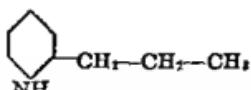
The process of isolation from plants or mixtures for the purpose of making preparations or assay is of primary importance to the pharmacist. While we cannot devote space here to a detailed description of the various methods employed, yet a few general remarks are in order. The alkaloids are usually contained in the plants in the form of salts, so they will be dissolved out if treated with an aqueous or hydroalcoholic menstruum. In order to insure complete extraction, about 1 per cent of tartaric acid may be added. We can also proceed on the idea of liberating the base by adding ammonia with a stronger alcohol or with some other organic solvent like ether or chloroform. Once having obtained the alkaloid in solution, it can be purified by successively transferring to dilute acid, making alkaline with ammonia, and withdrawing the base by an immiscible solvent. In toxicology and plant chemistry, where several bases may be encountered at the same time, frequent resort is made to the Stas-Otto modification of the original Dragendorff process of plant analysis. In this the acid solution is extracted successively by benzene, benzene, and chloroform, then the solution is made ammoniacal and again extracted in the same order. This will remove all common alkaloids except morphiae and eurarine.

The alkaloids are generally classified according to their derivation from pyrrolidine, pyridine, quinoline, isoquinoline, phenanthrene, or glyoxaline. It must be pointed out, however, that any compound which is a derivative of quinoline or isoquinoline can likewise be referred to pyridine. Furthermore, a substance like atropiae, classed in the pyrrolidiae group, in addition contains the nitrogen in a six-member ring. As a matter of fact, the

pyridine nucleus can be found in all of the common ones except pilocarpine, colchicine, histamine, and the purines. The plan usually adopted is to put in the pyridine class only those that contain the simple ring.

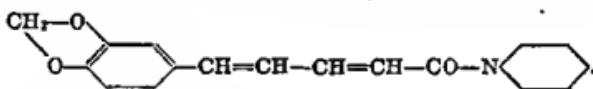
PYRIDINE

Coniine.—Conium or poison hemlock contains at least six bases. The one in largest amount is coniine, the simplest of common vegetable alkaloids, and the first one to be synthesized. Chemically it is α -propylpiperidine,



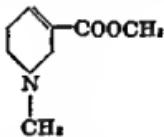
and was made by combining acetaldehyde with α -picoline and hydrogenating the product. It is a colorless, dextrorotatory liquid that is sparingly soluble in water and strongly basic. In properties it resembles nicotine very closely. The other bases of conium are: conhydrine, 4-hydroxyconiine; pseudoconhydrine, an isomer; N-methylconiine; γ -coniceine, having the formula of coniine but with a double bond in position 2; and ethylpiperidine.

Piperine.—The potent ingredient in pepper is piperine, which is N-piperylpiperidine



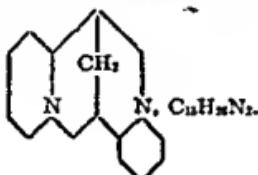
As might be expected in a compound with its nitrogen bound to carbonyl, it is a very weak base; indeed, it can be extracted from an acid solution, and its salts hydrolyze immediately. It is insoluble in water but can be split by boiling with acids into piperic acid and piperidine. Identification can be accomplished by the odor when oxidized to piperonal.

Arecoline.—There are five alkaloids in the areca nut, of which arecoline is the largest in amount. Arecoline is the methyl ester of N-methyl-1,5-tetrahydronicotinic acid



and is soluble in water and a strong base. Arecoline Hydrobromide N.F. is the form in which it is used, chiefly in veterinary practice. The other bases are: arecaine (arecaidine), the free acid; guvacine, like arecaine without the methyl group; guvacoline, N-methylguvacine; and arecolidine, an isomer of arecoline.

Sparteine.—The structure of sparteine, obtained from the hroom plant, is not certainly established, but it appears to be



It is a colorless liquid that has an odor like aniline, is insoluble in water, is basic to litmus, and is levorotatory. Sparteine Sulfate N.F. gives with ammonia and an ethereal solution of iodine a dark-green periodide.

Nicotine.—The alkaloid of tobacco is $\alpha(\beta\text{-pyridyl})\text{-N-methylpyrrolidine}$

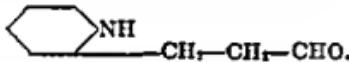


It is a colorless liquid, turning dark in the air, has a tobacco odor, and is levorotatory. Although it boils at 246° , it is volatile with steam, and distillation in this manner is the best way to isolate it. From the aqueous distillate it can be precipitated quantitatively by silicotungstic acid. Oxidation of nicotine breaks the pyrrolidine ring and results in the formation of nicotine acid.

For identification one can precipitate a red resin by ethereal iodine (Roussin) or use its physiological action on a frog. When a beaker is rinsed out with hydrochloric acid and then inverted over a sample of nicotine, the varnish-like hydrochloride is formed and crystallizes in a day or so. Coniine gives these same tests but with enough difference so that one can distinguish the two.

Tobacco also contains several other alkaloids in very small amount: nicotelline, nicotimine, isonicotine, nicotine, and nornicotine. The alkaloids of lobelia also belong in this class.

Pelletierine Tannate U.S.P. is a mixture of tannates from the alkaloids of pomegranate bark. Punicine or pelletierine, $3-(\alpha\text{-piperidyl})\text{propanal}$,



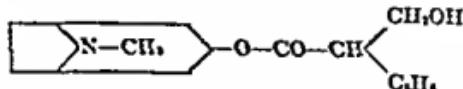
resinifies easily but its salts are fairly stable. Isopunicine, methylpunicine, and pseudopunicine are closely related to it in structure.

Eucaine Hydrochloride U.S.P., which is made synthetically, is the salt of 4-benzoxy-2,2,6-trimethylpiperidine.

PYRROLIDINE

Atropine U.S.P. is one of the five alkaloids obtained from plants of the *Solanaceae*, the others being hyoscyamine, scopolamine, apotropine, and helladonnine. The chief plants producing these are belladonna, hyoscyamus, scopolia, stramonium, and various other species of *Datura*. No one plant contains a single base unmixed with others of the group, and most of them yield several, even if only in small amount.

Chemically atropine is tropinyl tropate, the ester of the nitrogenous, secondary alcohol, tropine, with tropic acid.



Although the molecule contains an asymmetric carbon atom, the alkaloid is optically inactive and must be a racemic mixture. The active forms are hyoscyamine.

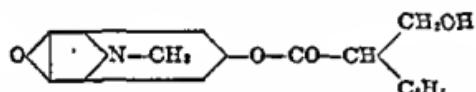
Atropine is a strong base; it is one of the few alkaloids that will reddens phenolphthalein, and it will precipitate red mercuric oxide from mercuric

chloride in alcoholic solution (Gerrard test). It is usually identified by the Vitali test, in which it is evaporated with nitric acid and alcoholic potassium hydroxide is added to the residue to give a fading purple color. The mydriatic response when instilled into the eye is characteristic and can be used for identification. It can be distinguished from hyoscyamine by the appearance and melting point of its double salt with gold chloride. Atropine Sulfate U.S.P. is the form in which it is most often used in medicine. In aqueous solution it is gradually hydrolyzed to tropine, so that such preparations should be freshly made.

Hyoscyamine, the optically active form of atropine, is obtained from hyoscyamus. It is contained in other drugs but is usually racemized during extraction; indeed, warming it with a little barium hydroxide will convert it completely to atropine. It gives the Gerrard test very slowly and can further be distinguished from the racemic form by the fact that the precipitate with gold chloride is lustrous and melts at a higher temperature.

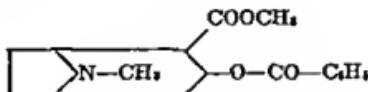
Homatropine Hydrobromide U.S.P., an artificial mydriatic, is the salt of tropinyl mandelate and, therefore, a homologue of atropine. The free base behaves very much like atropine but does not give the Vitali test. Homatropine Hydrochloride N.N.R. and Novatropine N.N.R. (Homatropine Methyl Bromide) are used as mydriatics.

Scopolamine Hydrobromide U.S.P. is a salt of scopolinyl tropate



The free base is very much like atropine in properties, except that it is not strong enough to give the Gerrard test. It is levorotatory; the racemic mixture was formerly called hyoscine, but this term is now used synonymously with scopolamine, and the name atroscine is given to the racemic form. **Scopolamine Stable N.N.R.** (Scopomannite) is a solution rendered stable by the addition of mannitol.

Cocaine U.S.P. is methylbenzoylecgonine, and ecgonine is a carboxyl derivative of tropine.

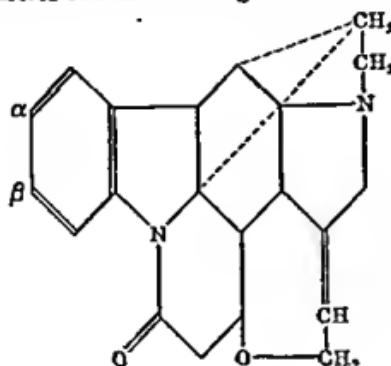


Being twice an ester, it is very easily hydrolyzed and should not be kept in solution for extended periods. However, the statement that such a solution cannot be sterilized by boiling is probably exaggerated; there may be some decomposition, but not enough to interfere with effective application. Upon hydrolysis it is converted to methyl alcohol, benzoic acid, and ecgonine. It can be identified by esterifying the benzoic acid to ethyl benzoate or the methyl alcohol to methyl salicylate. The best method in the right hands is to instil into the eye, where it causes mydriasis, blanching, and anesthesia, all of which can easily be determined. **Cocaine Hydrochloride U.S.P.** is the form usually used.

In coca leaves with the cocaine are several other interesting alkaloids: cinnamylcocaine, which contains cinnamic in place of benzoic acid; tropococaine or pseudotropinyl benzoate; α - and β -truxillines, which are dimo-

lecular products from cinnamylcocaine; hygrine, a simple pyrrolidine derivative; cuscohygrine; pseudococaine; and cocainidine.

Strychnine N.F. has a much more complicated structure and one that is not yet entirely certain. In the formula given the dotted lines indicate two alternate possibilities for that linkage.

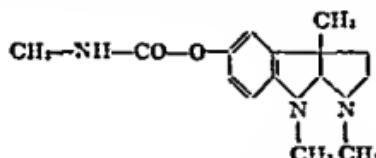


Strychnine is about the most stable of all alkaloids, as it can be distilled without decomposition at 5 mm. pressure. It can be heated on a steam bath with concentrated sulfuric acid without any action except to form a salt and, since most other bases are decomposed in this way, the process offers a good means for purification. Strychnine is further distinguished from the others by the facts that it is insoluble in ether and is much more bitter; one part in a million can be detected by taste. The so-called fading purple test is characteristic, although other alkaloids and mixtures may give results that are somewhat similar. It is conducted by drawing a crystal of potassium dichromate through the solution in sulfuric acid, when a fading purple trail follows the crystal. Injected into a frog, it gives an unmistakable hypersensitivity to outward stimuli, a characteristic test that can be used to identify.

The official salts are Strychnine Nitrate N.F., Strychnine Sulfate U.S.P., and Strychnine Phosphate N.F.

Brucine Sulfate N.F. is the salt of a second alkaloid occurring with strychnine in nux vomica. Its formula differs from that of strychnine in having two methoxy groups at the positions marked α and β in the formula given. Brucine gives with nitric acid a characteristic red color which can be changed to purple by stannous chloride. The reaction with nitric and nitrous acids is used to remove brucine from admixture with strychnine in the assay of nux vomica.

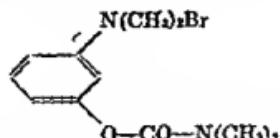
Physostigmine Salicylate U.S.P. (Eserine Salicylate) is the salt of eserine or physostigmine, an alkaloid found in the calabar bean. It contains two pyrrolidine nuclei in addition to an aliphatic nitrogen.



The alkaloid is so unstable that it easily acquires a red tint by oxidation to rubreserine, and other reagents produce a variety of colors. A blue is

formed when the base is evaporated with ammonia, and this becomes red if acidified. The addition of sodium carbonate or hydroxide to the aqueous solution of a salt produces a red color. Indeed, no special tests for identification are needed, because one works but a very short time with this base without discovering that fact.

Neostigmine Bromide U.S.P. (Prostigmine Bromide), the dimethylcarbamic ester of 3-hydroxyphenyl trimethylammonium bromide, was introduced into medicine to take the place of eserine.



It is presumed to be the effective constituent of physostigmine and to be much more stable. Neostigmine Methylsulfate U.S.P. has $-\text{O}-\text{SO}_2-\text{OCH}_3$ in place of the bromine.

REVIEW QUESTIONS

- What is the general solubility of alkaloids and their salts in water, alcohol, ether, and chloroform?
- Illustrate the formation of salts and double salts by equations, using R_2N for the alkaloid.
- Give the composition of the common alkaloidal precipitating agents, including the reagents of Mayer, Hager, Drngendorff, Marme, Scheibler, Wagner, and Sonnenchein.
- State the general method for isolating alkaloids from plants or preparations.
- Outline the Stas-Otto method of analysis. Which common alkaloids are not extracted in this way?
- What are the six classes of alkaloids whose structure is known?
- Write the formula of coniine. Where does it occur? What alkaloid does it resemble in properties?
- What two substances are obtained on the hydrolysis of piperine? When it is oxidized what is formed?
- What is the source of arecoline? Write the formula.
- Write the formula of nicotine. How can it be identified? What is formed from it on oxidation?
- What is the composition of pelletierine tannate? of eucaine?
- formulas. State the Gerrard and Vitali tests.
- What is obtained from cocaine on hydrolysis? Why should solutions be freshly prepared? How can cocaine be identified by instillation in the eye?
- In what two ways can the stability of strychnine be shown? Describe the fading purple test.
- What structural relation does brucine bear to strychnine? What is its reaction with nitric acid?
- Why do we need no special test for eserine? Describe the reactions with sodium hydroxide and evaporation with ammonia.
- What is neostigmine and for what is it used?

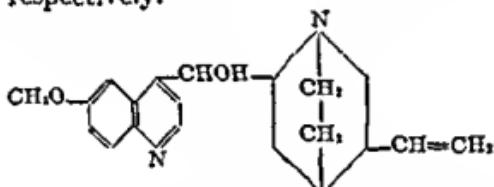
CHAPTER XL

ALKALOIDS (CONTINUED)

QUINOLINE

THE most important alkaloids that are in the quinoline class are those obtained from cinchona bark. This drug contains more than thirty bases, which appear to be very closely related to each other in structure, but only four are used in medicine, together with artificial derivatives of another. The two most often used are quinine and quinidine, the two other official ones are cinchonine and cinchonidine, and the fifth is cupreine.

Quinine U.S.P. and Quinidine N.N.R. are optical isomers, being the levo and dextro forms respectively.



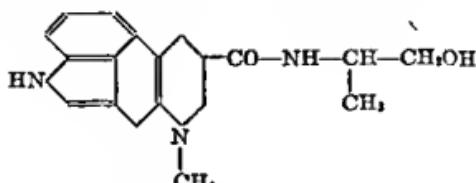
In the formula one notes an ethylene linkage, which should be easily affected by oxidizing agents, a secondary alcohol between rings, and the methoxyl radical. By the action of bromine water on a dilute solution, followed by the addition of ammonia, either alkaloid or its salts gives the bright-green color of thalleioquin. This is also given by other bases of cinchona but not by cinchonine or cinchonidine. Another characteristic reaction of the two is a blue fluorescence when dissolved in excess of diluted sulfuric acid. Quinidine differs from quinine in giving a precipitate with potassium iodide in fairly dilute solution.

Quinine Sulfate U.S.P., the salt most often used, is notable in being almost insoluble in water (1:810). Quinidine Sulfate U.S.P. can be dissolved to the extent of 1 gram to about 90 cc. of water. A number of other salts of quinine are also employed; in the Pharmacopœia are given the bisulfite, the hydrochloride, the dihydrochloride, the ethyl carbonate (euquinine), and the double salt with urea hydrochloride; the formulary describes the hydrobromide, the phosphate, and the salicylate. Altogether, more than a million pounds of quinine are isolated and used annually, much more than of any other alkaloid.

Cinchonine Sulfate N.F. and Cinchonidine Sulfate N.F. are the salts of optically isomeric alkaloids, the former being dextro and the latter levo. They have the same formula as quinine without the methoxy group, but they give neither the thalleioquin nor fluorescence test and in other ways are easy to distinguish from the other bases. They both give a bronze precipitate with an alcoholic solution of iodine (herepathite test), as do also quinae and quinidine but not cupreine. Cinchonidine differs from cinchonine and other bases in giving a precipitate with tartrates, while the sulfate of cinchonine can be distinguished by its solubility in chloroform.

Cupreine is the phenolic base of quinine or, in other words, has a hydroxy group in place of the methoxy. Consequently, it dissolves in either acids or bases, a fact which serves to distinguish it from the other alkaloids of cinchona. Hydrocupreine, made by reducing the ethylene linkage in eupreine, is made into various ethers to be used as substitutes for quinine, chiefly in pneumonia. Ethylhydrocupreine Hydrochloride N.F. (Optochin), the ethyl ether, shows neither the phenolic character of cupreine nor the easy oxidizability of quinine, but it gives the thalleioquin test. Eucupine is an isoamyl ether.

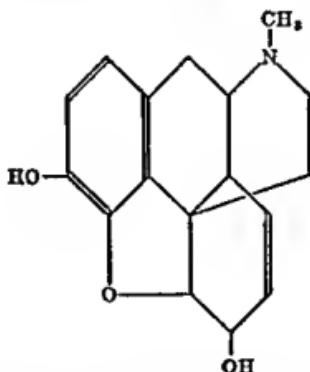
The only other important alkaloid in this class is ergonovine from ergot.



Ergonovine Maleate U.S.P. is dextro and not very soluble in water or alcohol. Ergotoxine ethanesulfonate, used as an official reference standard and Ergotamine Tartrate U.S.P. (Gynergen) are salts of other ergot alkaloids. These and several other bases found in the drug are apparently similar in structure, because they give the same degradation products, but they are much more complicated.

PHENANTHRENE

This group includes bases of opium and a few others that are relatively unimportant. About twenty-five alkaloids have been isolated from opium, which contains about 10 to 12 per cent of morphine, the chief base. Of the total amount of alkaloids, constituting about 25 per cent of opium,



more than 90 per cent is made up by morphine, narcotine, codeine, and papaverine. Of those used in medicine, morphine and codeine are in the phenanthrene class, while papaverine and narcotine are isoquinoline derivatives.

Morphine, being a phenol, is soluble in bases as well as acids, but it differs from all other alkaloids in that it is insoluble in water, ether, or chloroform. On account of its phenolic character and also of the secondary alcohol group, it is very easily oxidized by even mild agents, furnishing

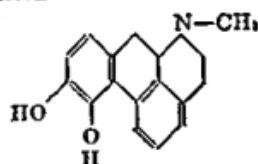
many interesting color reactions for identification. It can be acylated to a diacetyl compound, dehydrated by hydrochloric acid to apomorphine, or made into methyl or ethyl ether, some of the products being important drugs. Morphine Sulfate U.S.P. is said to be the most useful of all drugs, but Morphine Hydrochloride N.F. is occasionally employed also.

In identifying the alkaloid many characteristic tests are available, of which the Pharmacopœia lists a few. Not included is one devised by LeFort that has proved best in the writer's experience, although one should never depend wholly upon one. In this test, the dry sample of alkaloid on a spot plate is covered with iodic acid (2 per cent), the iodine liberated by oxidation of the morphine is washed away with chloroform, and ammonia water is added to give a mahogany-brown color. The official tests with molybdic acid (Froehde), formaldehyde (Marquis), ferric chloride, and selenous acid are often employed.

In Codeine U.S.P. the phenolic hydroxyl has been converted to a methyl ether, and no longer do we find such easy oxidation or any solubility in alkali. This is, of course, also true of the salts, Codeine Sulfate U.S.P. and the much more soluble Codeine Phosphate U.S.P. Codeine behaves somewhat like morphine in the identification tests, but it does not give those with ferric chloride and iodic acid. The insolubility in alkali furnishes a method for separating it from morphine.

The corresponding ethyl ether (dionine) is employed in the form of Ethylmorphine Hydrochloride U.S.P. It is similar to codeine in reactions but differs in its solubility in water. Ammonia water precipitates it from the salts in fairly dilute solution, while codeine remains in solution at the same concentration.

Apomorphine Hydrochloride U.S.P. is obtained from morphine by dehydration with hydrochloric acid.



Since it is a diphenol, the free base is very readily oxidized, much more easily than morphine, and in the crystalline state or in solution is liable to turn green. Nitric acid dissolves the salt to give a dark-purple solution, while iodine with sodium bicarbonate produces an emerald-green color, from which ether extracts a red substance. Ammoniacal silver nitrate is almost immediately reduced to black metallic silver. As in the case of eserine, any work with this alkaloid is soon recognized because of the various colors that can be obtained with reagents.

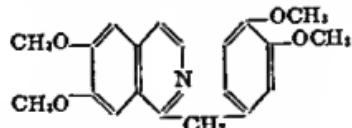
Diacetylmorphine (heroin) has been prohibited in commerce because it is a dangerous drug and induces a more vicious habit than does morphine. Occasionally, however, one encounters the illegal drug. It is very easily hydrolyzed and then gives tests for morphine and for acetic acid. The analyst must be very cautious in extracting it, if heroin is to be a product of the process.

Dihydromorphinone Hydrochloride U.S.P. (Dilnudid) is obtained from morphine by hydrogenation of the double bond and oxidation of the secondary alcohol to a ketone. The melting point of the oxime is a good

means for identification. Dicodid, the methyl ether, has likewise been proposed for use.

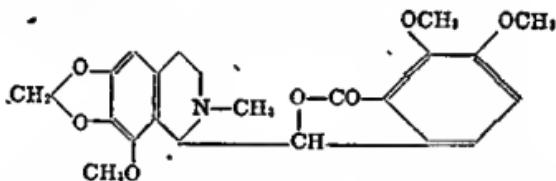
ISOQUINOLINE

Papaverine N.N.R. is a tetramethoxybenzylisoquinoline.

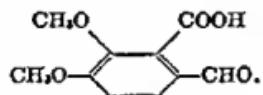


It is the fourth alkaloid of opium, where it is found to the extent of nearly 1 per cent. Its relaxing action on muscles is presumed to be attributable to the benzyl grouping, and this led several years ago to the introduction into medicine of several benzyl esters, like the benzoate. The most characteristic reactions of papaverine are the production of a lemon-yellow precipitate with ferricyanides, and the change in color to rose and brown when treated with a solution of formaldehyde in sulfuric acid (Marquis). Papaverine Hydrochloride N.F. is occasionally employed in medicine.

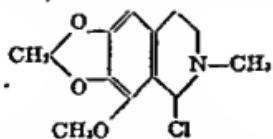
Narcotine (Anarcotine), the second alkaloid of opium, is a gamma lactone with a nucleus similar to that of papaverine.



It is employed industrially in the manufacture of cotarnine by oxidation with nitric acid. If it is heated with barium hydroxide or sulfuric acid at 140°, it is converted to hydrocotarnine and opianic acid.



The base, cotarnine, which was mentioned as obtainable from narcotine by oxidation, is used in medicine in the form of Cotarnine Chloride N.F. (Stypticin).



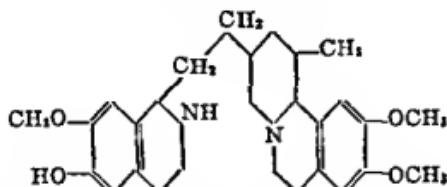
Narceine, cryptopine, and laudanine are alkaloids of opium that are similar to narcotine in structure.

Hydrastine Hydrochloride N.F., a salt of the chief alkaloid of hydrastis, has the same formula as narcotine without the methoxy group in the isoquinolinc nucleus. When it is heated with barium hydroxide or sulfuric acid, it is converted to opianic acid and hydrastinine. The latter has been used like cotarnine and hydrastine in medicine.

Berberine from berberis, canadine from hydrastis, and the alkaloids

from corydalis have structures very much like that of hydrastine and nareotine. In this class also belong the chief bases of sanguinaria and calumba.

The alkaloids of ipecae are somewhat more complicated in structure, but they contain the isoquinoline nucleus.

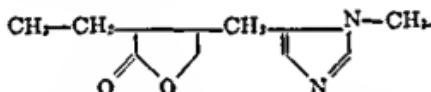


The formula given is for cephaeline, which is phenolic and soluble in alkalies, making it easy to distinguish from emetine which is its methyl ether. Emetine Hydrochloride U.S.P. gives with Froehde's reagent (molybdic oxide in sulfuric acid) a bright-green color.

GLYOXALINE

The nucleus of imidazole or glyoxaline is found in pilocarpine and other alkaloids of pilocarpus leaves, also in histamine which has already been described.

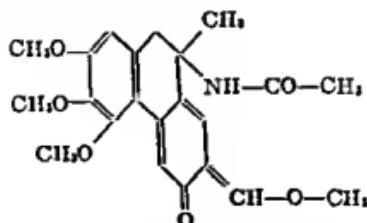
Pilocarpine Nitrate U.S.P. and Pilocarpine Hydrochloride N.F. are sometimes used to counteract atropine or to induce perspiration. The alkaloid is a gamma lactone with the formula



It is easily distinguished by the Heleb test; a solution of less than 20 milligrams is mixed with hydrogen peroxide and benzene, and a few drops of potassium dichromate are added, giving a yellow solution and a violet color in the benzene. Isopilocarpine, pilocarpidine, and isopilocarpidine are other alkaloids that are found in the leaves.

UNCLASSIFIED

Colchicine U.S.P. contains the phenanthrene nucleus, but the nitrogen is not cyclic and the compound is so much different from morphine that it is classed separately.

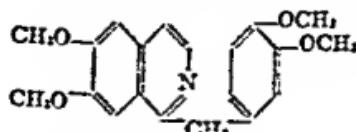


It will be observed that the formula shows an orthoquinone structure, which accounts for the yellow color of the substance, intensified by acids.

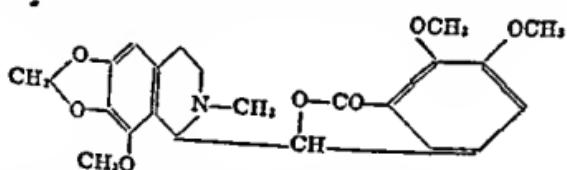
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ISOQUINOLINE

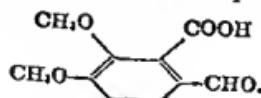
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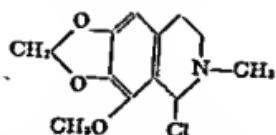
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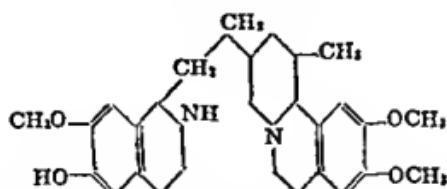
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The alkaloids of ipecac are somewhat more complicated in structure, but they contain the isoquinoline nucleus.

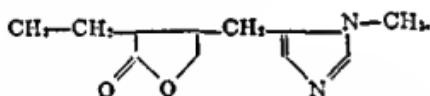


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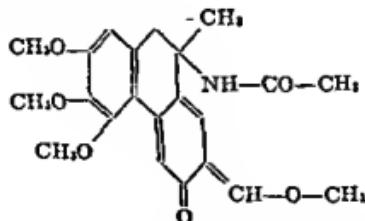
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UNCLASSIFIED

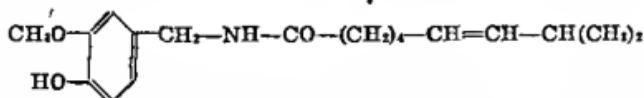
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It will be observed that the formula shows an orthoquinone structure, which accounts for the yellow color of the substance, intensified by acids.

Colbicicine differs from other alkaloids in being a very weak base, so that it can be extracted from acid solution, and in being soluble in water. The addition of nitric acid to the yellow solution in sulfuric acid converts the color to greenish-blue, rapidly changing to red and then to the original yellow. If an excess of sodium hydroxide is now added, the color changes to red. Chloroform unites with it to form a crystalline, molecular compound, which may be found as an adulterant.

Capsaicine, the pungent principle of capsicum, is likewise an acid amide, as well as a phenol.



It is insoluble in water but dissolves in organic solvents or in alkalies.

Other substances that have already been described might be placed in this group, depending upon whether or not one classed them as alkaloids. As examples might be mentioned ephedrine, epinephrine, muscarine, and choline.

UNKNOWN STRUCTURE

Aconitine, used as an official reference standard, is $\text{C}_{34}\text{H}_{47}\text{NO}_{11}$ or acetylbenzoylaconine, and upon hydrolysis gives aconine, acetic acid and benzoic acid. Due to the ease with which this reaction takes place, various samples of aconite are often found to differ enormously from the normal strength, and this unreliability has led to much decreased use. Other species of aconite contain aconitines that are different but probably of similar structure.

Veratrum Viride contains a number of bases, chief of which are protoveratrine, $\text{C}_{32}\text{H}_{51}\text{NO}_{11}$, and jervine, $\text{C}_{26}\text{H}_{43}\text{NO}_3$. The physiological action of any of these is not completely like that of the crude drug, which is similar to aconite. Veratrine, obtained from sabadilla seeds which have no relation to veratrum, is a mixture of alkaloids, mainly cevadine, $\text{C}_{32}\text{H}_{49}\text{NO}_9$.

A few less important drugs contain alkaloids as the active components. The structure of some of these is known, but there is no need to present them in detail here. For further information the student is referred to the dispensatory and especially to Henry, "Plant Alkaloids." The following list of these drugs and a few other interesting plants is not intended to be completely informing.

<i>Plant</i>	<i>Alkaloids</i>
Gelsemium	Gelsemine $\text{C}_{21}\text{H}_{21}\text{N}_1\text{O}_2$
Larkspur	Delphinine $\text{C}_{24}\text{H}_{31}\text{NO}_3$ and others
Calumba	Jateorrhizine $\text{C}_{21}\text{H}_{21}\text{NO}_2$ Columbamine, an isomer
Sanguinaria	Sanguinarine $\text{C}_{21}\text{H}_{21}\text{NO}_4$, forming red salts
Lobelia	Lobeline $\text{C}_{21}\text{H}_{21}\text{NO}_2$
Curare	Curarine $\text{C}_{18}\text{H}_{21}\text{N}_1\text{O}$
Aspidosperma	Yohimbine $\text{C}_{21}\text{H}_{21}\text{N}_1\text{O}_2$
Anhalonium	Anhalonine $\text{C}_{21}\text{H}_{21}\text{NO}_3$ and several others
Angostura	Cusparine $\text{C}_{21}\text{H}_{21}\text{NO}_3$
Alstonia	Alstonine $\text{C}_{21}\text{H}_{21}\text{N}_1\text{O}_2\text{N}_1$

REVIEW QUESTIONS

1. What is the relation of quinine to quinidine? of cinchonine to cinchonidine?
2. Which of the cinchona alkaloids give the thalleioquin and fluorescence tests? Describe the tests.
3. How can cinchonine and cinchonidine be distinguished from other cinchona bases and from each other?
4. How can ethylhydrocupreine be distinguished from them?
5. In what respect does morphine differ from all other alkaloids? How can it be separated from codeine? What is formed on dehydration? on acetylation?
6. Describe the LeFort and two other tests for morphine and codeine.
7. Why is apomorphine so unstable? Describe its reactions with nitric acid and with iodine.
8. What is heroine? dilaudid? dicodid?
9. What is the reaction of papaverine with ferrocyanides and with the Marquis reagent?
10. How is narcotine converted to cotarnine? What are formed on heating narcotine with barium hydroxide?
11. How does hydrastine differ structurally from narcotine? How does it behave with barium hydroxide?
12. What relation has emetine to cephaeline? How could the two alkaloids be separated?
13. Describe the Helch test for pilocarpine.
14. What is the effect of acid on the color of colchicine? Why is there an official test for chloroform? Describe the successive action of sulfuric acid, nitric acid, and sodium hydroxide on colchicine.
15. In what respect is capsaicin like colchicine?
16. Name the three important alkaloids of ergot.
17. What substances are formed when aconitine hydrolyzes?
18. Name the alkaloid in veratrum viride, gelsemium, larkspur, calumba, sanguinaria, and Iohelia.



CHAPTER XLI

DYES

THE subject of dyes is an important one because of the thousands that are made and used and also because of the great variety. A tremendous industry has been built up in this field, and hundreds of chemists are continuously working to devise new compounds and improve old processes. There is an added significance to the physician and pharmacist in the fact that many dyes are bacteriostatic or have some other useful action on or in the body. In addition, the pharmacist is immensely interested in stains for bacteriology, botany, and pathology, and the number so used has increased enormously in recent years.

The reason why some substances are colored while most others are not is, as we know from our study of physics, because the colored substance absorbs certain portions of the visible spectrum. As a matter of fact, all organic substances absorb certain wave-lengths of light and thus give a so-called absorption spectrum. The particular wave-lengths taken up by a colorless compound lie in the ultraviolet zone and must be studied by a photographic plate or some other agency or instrument that is sensitive. The relation between the absorption spectrum and chemical structure is well enough known so that a question between two formulas for a compound can often be settled by determination of the wave-lengths it will take up.

It is evident, therefore, that only compounds of particular structure will be colored. Witt, in 1876, suggested that we call the particular groupings chromophores and the colored substance a chromogen. The usual important chromophores are nitroso, —NO ; nitro, —NO_2 ; an azo linkage, $\text{—N}_2\text{—}$, between aromatic groups; the quinoid structures,  and ; diketones, —CO—CO— ; and unsaturated ketone groups in cyclic compounds, —C=C—C=O— .

In order to be a dye, such a chromogen must adhere to the textile regardless of rinsing and washing, and unfortunately many beautifully colored substances will not do this. Those that contain certain substituent groups, which Witt called auxochromes, are endowed with the power to dye silk and wool directly and sometimes cotton. The true auxochromes are basic and include —NH_2 , —NHR , and —NR_2 ; the color is practically always deepened by their introduction. The acid auxochromes, which lighten the color, are $\text{—SO}_2\text{OH}$, —COOH , and —OH .

The dyer classifies his materials according to processes rather than chemical structure. The most important group is that of vat dyes which will be described under indigo, and the second class of sulfur colors is one of the groups to be discussed. The direct cotton dyes are certain ones of the bisazo class. The direct acid and basic dyes, chiefly azo, are those that are applied to fabrics by digesting in boiling solution, and the mordant

dyes are usually of the anthraquinone group. Finally, ingrain colors and developed dyes are formed in the process of applying and are most often in the azo class.

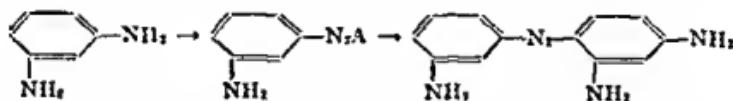
It will be impossible here to go very far into the chemistry, as there are thousands of compounds used. The chemical nomenclature is so complicated that trade names are usually employed, and even these are quite confusing. Attempts were made years ago to catalogue the structure and number the compounds, and two such lists are at present used, one by Schultz and Julius and the other by the Society of Dyers and Colorists. Unfortunately, the numbers in these two do not coincide. All that we can do in such a complicated subject is to take up each class generally and give a few illustrations, including whatever compounds are important in medicine or in the laboratory.

The nitrophenols are simple acid dyes that were formerly much used, but they are of little importance today. Some of them are useful in coloring pharmaceutical preparations or foods. The best illustrations of the class are picric acid; Martius yellow, 2,4-dinitroalphanaphthol; naphthol yellow S, its sulfonate; and fast green O, 2,4-dinitroresorcinol.

AZO DYES

All of the compounds in this class are prepared by coupling of a diazonium salt with phenols or amines, as was noted in an earlier chapter. The chromophore is the azo linkage and the amino and phenol groups are auxochromes. The compounds are all derivatives of azobenzene and named accordingly; their structure can be determined by reduction, which splits them at the azo group to form two amines. The azo dyes are classified into acid, basic, and mixed, depending on what the auxochromes are. Frequently, especially for dyeing on cotton, the diazotization is performed in the cloth (developed dyes) or the coupling is carried out there (ingrain process).

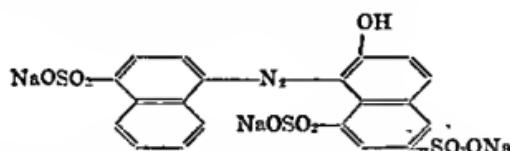
The chrysoidines or basic azo dyes are usually applied in the form of salts. Aniline yellow, the simplest and the first one that was made, is p-aminoazobenzene, and its dimethyl derivative is called butter yellow. Chrysoidine, made by coupling benzenediazonium salt with m-phenylene diamine, has a second amino group. Bismarck brown, commonly employed in the leather trade, is prepared by diazotizing m-phenylene diamine.



The reaction goes on so easily that the amine can be used to detect traces of nitrous acid. Serenium, used as a urinary antiseptic, is p-ethoxyphenyl-
made by diazotizing p-phenetidine

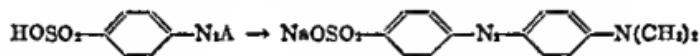
more important because they are usually direct; most of them are sodium salts of sulfonic acids. Orange I is from diazotized sulfanilic acid and alphanaphthol, while Orange II is prepared in the same way from betanaphthol. Orange II is made in the largest amount of all azo dyes, constituting about one-eighth of the total.

Resorcin yellow or tropaeolin O uses resorcinol in the same reaction. Orange G, an official reagent, is sodium azobenzenehetanaphtholdisulfonate, $C_6H_5-N_2-C_{10}H_5(OH)(SO_2ONa)_2$ 2:6:8. Amaranth U.S.P. (Fast Red, Bordeaux-S) is used for coloring preparations.

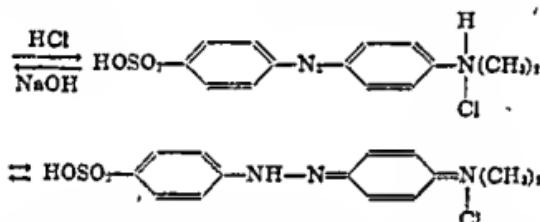


Para red, an ingrain color, is made in the fabric, which is first dipped in a solution of betanaphthol and then in a diazonium solution from p-nitraniline.

Examples of mixed azo dyes are the acid-base indicators, methyl orange and methyl red. The former is the sodium salt of helianthin, made by diazotizing sulfanilic acid and coupling with dimethylaniline.

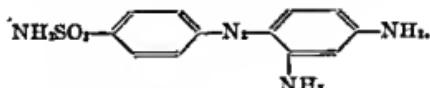


The color change when this is treated with an acid is due to rearrangement to quinoid structure.

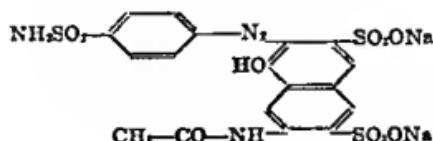


Methyl red, made similarly from diazotized anthranilic acid, undergoes the same sort of changes with acid and base.

The dyes which led to discovery of the virtues in sulfanilamide are also in this class. Prontosil, which may be taken as illustrative, was prepared by coupling m-phenylene diamine with diazotized sulfanilamide, giving the formula

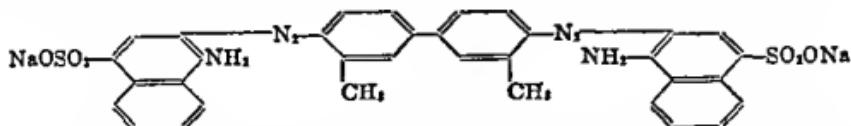


Neoprontosil, now most often used, is

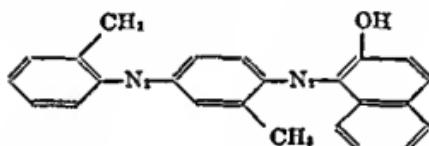


In general the compounds in this group contain the radical $\text{NH}_2\text{SO}_2-\text{C}_6\text{H}_4-\text{N}_2-$ and upon reduction, as takes place in the body, are converted to sulfanilamide.

The bisazo dyes can, for some unknown reason, frequently be applied directly to cotton. They have more than one azo and can be made, either by diazotizing an azobenzene derivative, or by coupling an amine or phenol with a diazotized diamine. A good illustration is benzopurpurin 4B,



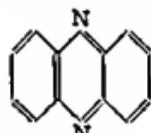
made by diazotizing dimethylbenzidine and coupling with naphthionic acid. Congo red, an official reagent and a direct cotton dye, is made in the same way from benzidine. Resorcinol Brown N.F. is the sodium salt of an acid bisazo dye. Scarlet Red N.F. (Biebrich Scarlet), tolylazotolylazo-betanaphthol, has the formula



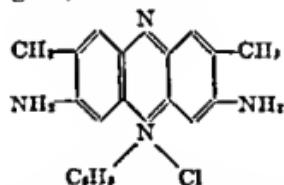
Scarlet Red Sulfonate N.N.R. is used in medicine similarly, as is also Dimazon N.N.R. which is a simple azo compound.

SAFRANINES

These are derivatives of azophenylene or phenazine,



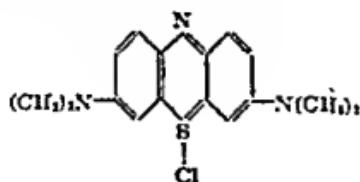
Safranine O, an official reagent, is



Neutral red, also a reagent, has a like structure, and the first of all artificial dyes, Perkin's mauve made by oxidizing aniline, is of this class.

Oxazines and thiazines, in which one nitrogen is substituted by sulfur or oxygen, are also used. Brilliant cresyl blue, another formulary reagent, is of the oxazine type.

Methylthionine Chloride U.S.P. (Methylene Blue) is a thiazine



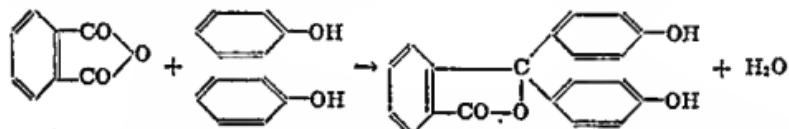
made by the action of ferric chloride on p-aminodimethylaniline and carbon disulfide. When it is treated with nitrous acid, there is formed methylene green. Other such reagents of this class are toluidine blue, azur A, azur II, and azur II eosin.

SULFUR DYES

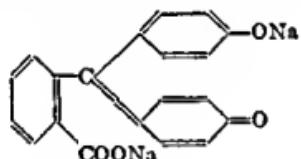
The manufacture of sulfur dyes is often a trade secret and, even if the method of preparation is known, the composition is usually a mystery. In general they are made by heating amines or phenols with sulfur and sodium sulfide at about 200°. The products are insoluble in water but are soluble in sodium sulfide, which must be used in the bath. They are applied mostly as vat dyes, but the reduced leuco compounds are colored. Sulfur black, second only to indigo in importance, is prepared from 2,4-dinitrophenol or picric acid.

PHTHALEINS

Phenolphthalein U.S.P., the prototype of this class, is made by heating phenol with phthalic anhydride.



It is a colorless powder that is insoluble in water but soluble in alcohol. When it is made alkaline with sodium hydroxide, the red sodium salt is produced, the necessary chromophore being a quinoid structure formed by rearrangement.



Reducing agents convert phenolphthalein to phenolphthalin, which is used as a test for oxidases and for blood.

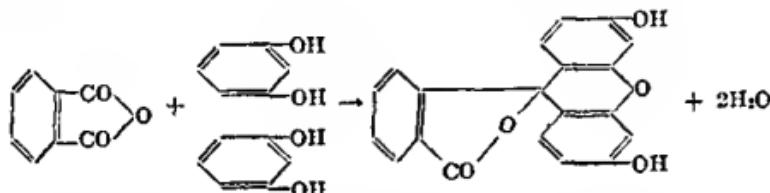
A similar method of preparation can be used to make thymolphthalein, cresolphthalein, and naphtholphthalein, used as indicators.

Several di- and tetra-halogen derivatives are made by starting with substituted phthalic anhydride or substituted phenol. They are named by placing the halogen in the appropriate place in the title of the parent compound; for example, tetrachlorophenolphthalein indicates four chlorine atoms in the phenol radical, while phenoltetrachlorophthalein has the halogen in the phthalic nucleus.

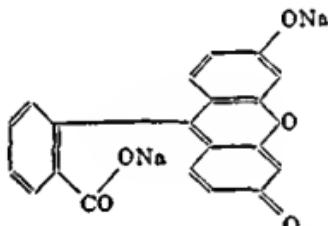
Phenoltetrachlorophthalein N.N.R. is used to test functioning of the liver, as is also Sulphromophthalein Sodium U.S.P., the sodium salt of phenoltetrachromophthalcindisulfonic acid. Sodium phenoltetraiodophthalein is employed for the same purpose and as X-ray contrast medium under the titles of Phentetiothalein Sodium N.N.R. and iso-ideikon. Iodophthalein Sodium U.S.P. (Iodeikon), the sodium salt of tetraiodophenolphthalein, is an X-ray medium in cholecystography.

Phenolsulfonphthalein U.S.P. (Phenol Red) has SO₂ in place of CO in phenolphthalein and is manufactured with o-sulfobenzoic acid instead of phthalic anhydride. It is an indicator of the same type and is used to test functioning of the kidneys. Bromophenol blue, which is the tetrabrom (phenol) derivative, and bromothymol blue or dibromothymolsulfonphthalein are useful indicators, as are also thymol blue or thymolsulfonphthalein, bromoresol purple or dibromo-o-cresolsulfonphthalein, and bromoresol green or tetrabromo-m-cresolsulfonphthalein.

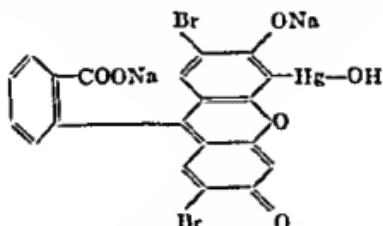
Fluorescein N.N.R. (Resorcinolphthalein) is manufactured by the action of phthalic anhydride on resorcinol; the hydroxyl groups of the latter also dehydrate.



The compound without the hydroxy groups, fluoran, is formed from phenol if the attack is in ortho position and is a by-product of phenolphthalein manufacture. Fluorescein is dihydroxyfluoran. Fluorescein Sodium U.S.P. is the sodium salt.



Eosin Y, a beautiful red dye and an official reagent, is the sodium or potassium salt of tetrabromofluorescein, the halogen being in the resorcinol molecule. It is used with a mordant to dye cotton and directly on silk and wool, also to make red ink. Other dyes in this class are the official reagents ethyleosin, diiodofluorescein, pyronin Y, and rose bengal. Merbromin N.F. (Mercurochrome) is the sodium salt of dibromohydroxymercurifluorescein.



TRIPHENYLMETHANE

Michler's ketone, made by the action of dimethylaniline on phosgene, is a derivative of diphenylmethane. It is produced in enormous quantities

all of them can be split by boiling with dilute acids, although further changes may take place in the aglucone or even the sugar. Alkalies may bring about hydrolysis but very frequently have undesirable secondary actions. The best method is by means of a specific enzyme, if a proper one can be selected. In general, maltase or zymin will suffice for alpha compounds and emulsin for the beta, which is the usual form in nature. In many plants that contain glycosides, this is accompanied by a specific enzyme which is segregated in separate cells. It has been postulated that the function of glycosides is to protect; when the plant is injured the enzyme hydrolyzes the compound to furnish the antiseptic aglucone. It is certainly true that the aglucones are often bacteriostatic, even if not bactericidal.

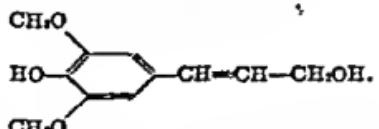
The synthesis of many natural and artificial glycosides has been accomplished. The first was of salicin by Michael in 1879, who treated the potassium salt of salicylic aldehyde with the product of action of acetyl chloride and d-glucose. The product was an artificial glucoside, helicin, which furnished salicin on reduction. A general method for preparing, devised by Emil Fischer, is to dissolve the sugar in the alcohol and pass in dry hydrogen chloride. When the sugar is insoluble in the alcohol, acetyl derivatives may be made, as they are usually soluble in benzene or chloroform. Alcohols of all kinds, including those of the aromatic and alicyclic classes, have thus been converted to glycosides, and the method is successful even with hydroxy acids like lactic. Various sugars have also been used, although disaccharides are apt to hydrolyze because of the hydrochloric acid formed.

Any detailed classification of these compounds is never satisfactory, again because of the great variety. We can segregate a group like the saponins, or those furnishing hydrocyanic acid, or those containing sulfur, but in any case the great bulk of glycosides remains unclassified. One might separate the natural ones on the basis of chemical structure of the aglucones, which are cyclic and generally aromatic, but unfortunately the composition of many is unknown.

In the list which follows have been placed a few of the natural glycosides that are of interest to the pharmacist, together with the products of hydrolysis if these are known. Some of them have already been mentioned in preceding pages, and no formulas of aglucones are given when these have been described previously.

Coniferin, occurring in asparagus, beets, sugar-cane, and especially in the sap of conifers, furnishes with emulsin dextrose and coniferyl alcohol, but with acids a resin. Vanillin is the product if it is oxidized with chromic acid, but potassium permanganate changes it to glucosides of vanillin or vanillic acid.

Syringin, from the bark of syringa and privet, gives dextrose and syringyl alcohol, which is 3-methoxyconiferyl alcohol or



Salicin N.F., in willow and some species of poplar, is split by the enzyme salicase to dextrose and saligenin. Its synthesis has already been described.

Populin, from aspen and other poplars, is benzoysalicin; in fact, it can be made by benzoylation of salicin. Emulsin does not affect it, but acids give dextrose, benzoic acid and saligenin.

Helein, obtained artificially as previously noted, is an oxidation product of salicin and on hydrolysis yields dextrose and salicylic aldehyde.

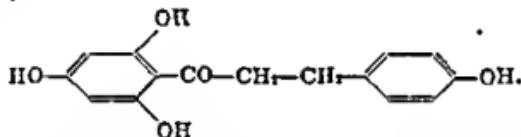
Gaultherin, of wintergreen and other plants, is hydrolyzed by maceration with water and steam distillation to dextrose and methyl salicylate.

Salinigrin, occurring in the bark of several willows, gives dextrose and p-hydroxyacetophenone.

Arhutin, which has been found in *Uva ursi* and many other ericaceous plants, when boiled with dilute acids furnishes dextrose and quinol. Methylarhutin, yielding methylhydroquinone, is also a constituent of some of the same plants.

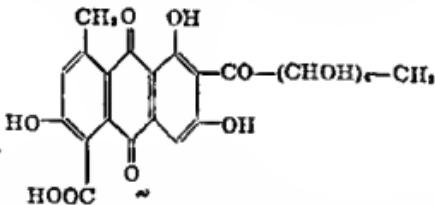
Quereitrin, from the bark of a species of oak, the quercitron, gives rhamnose and quercetin.

Phlorhizin (phlorizin), $C_{21}H_{22}O_{10} \cdot 2H_2O$, is obtained from the root-bark of several rosaceous fruit trees, including apple, plum, and cherry. It hydrolyzes by boiling acids to dextrose and phloretin. The latter, which appears to be also uncombined in the root-bark of the apple, is a derivative of phloroglucinol,



Aesculin (esculin, esculinie acid), from the inner bark of the horse-chestnut, yields dextrose and 3,4-dihydroxycoumarin (esculetin) with either acids or emulsin.

Carminic acid, the coloring matter of cochineal, is a purplish-red powder that is soluble in water or alcohol. On boiling with dilute acids, it is converted to carmine-sugar, a methyl pentose, and carmine red, an anthraquinone derivative. Carminic acid has the formula,



Like other anthraquinone derivatives, it forms lakes with metallic hydroxides. Its aluminum lake is Carmine N.F., which is only slightly soluble in water but dissolves in ammonia and alkalies to a purplish red solution.

The various emodin drugs contain glycosides that hydrolyze to emodin and a sugar that depends upon the drug. Aloin U.S.P. furnishes arabinose, Ruherythric acid from madder purin of the root is from another glycoside.

Idaein, the red color of apples and other fruit, is split into galactose and the colored compound, cyanidin.

Composition of aglucones of the digitalis group has been discussed in

a previous chapter.¹ Digitoxin, $C_{41}H_{54}O_{13}$, yields digitoxigenin, $C_{23}H_{34}O_4$, and three molecules of digitoxose, $CH_3-(CHOH)_2-CH_2-CHO$. Digitalin German N.N.R and Digitaline Nativelle N.N.R. are said to give dextrose, digitalose, and digitaligenin, bnt are probably mixtures. The same may be said of Gitalin N.N.R., although a glycoside by this name, $C_{35}H_{56}O_{12}\cdot 2H_2O$, has been separated from the drug. Digitalanid N.N.R. is a mixture obtained from *Digitalis lanata*, which are closely related in structure to those from the official species.

Strophanthin U.S.P. is a mixture containing chiefly $C_{36}H_{54}O_{14}\cdot 2H_2O$. This hydrolyzes to strophanthidin, a dilactone, and a strophanthobioside, which gives dextrose and cymarose, $CH_3-CHOH-CHOH-CH(OCH_3)-CH_2-CHO$. Ouabain U.S.P. (Crystalline Strophanthin), $C_{29}H_{44}O_{12}\cdot 8H_2O$, cleaves to ouabagenin, $C_{22}H_{34}O_8$, and rhamnose. Antiarin, $C_{27}H_{42}O_{10}$, gives a methyl pentose and antiarigenin.

Squill contains several glycosides, but exact knowledge of these is lacking. Scillaren N.N.R. and Urginin N.N.R. are presumed to contain active compounds. Adonis, apocynum, convallaria, and other drugs may contain similar glycosides.

Until recently the saponins of drugs have been very little known, except for doubtful empirical formulas. We have already mentioned the few cases in which the aglucones have been investigated. Digitonin is given the formula $C_{45}H_{90}O_{29}$ and furnishes four molecules of galactose and digitogenin, $C_{27}H_{44}O_8$. The compounds from sarsaparilla, trillium, and a few other drugs are known to be similar.

Glycyrrhizin of licorice, $C_{44}H_{66}O_{18}N_2$, is the ammonium salt of glycyrrhizic acid, which hydrolyzes to glycyrrhetic acid, $C_{22}H_{44}O_4N$, and parasaccharic acid.

Indican in woad and the indigo plants, furnishes indoxyl and dextrose. This is not to be confused with the indican of urine.

Solanine, a glyco-alkaloid from potato sprouts and other solanaceous plants, hydrolyzes to dextrose and solanidine, $C_{28}H_{44}O_2N$.

There are four cyanogenic glucosides yielding benzaldehyde. From them it is possible to isolate the intermediate mandelonitrile, made up of benzaldehydc and hydrocyanic acid. The dextro form of mandelonitrile is furnished by prunasin of wild cherry, the levo by sambunigrin from sambucus, and the racemic form by prulaurasin of cherry laurel. Amygdalin of the bitter almond differs from these in furnishing twice as much dextrose per molecule.

Sinigrin, found in the seeds of black mustard, is potassium myronate, $C_{10}H_{16}O_9NS_2K$. When it is hydrolyzed by myrosin, an enzyme found in the seed but chiefly in white mustard, it yields dextrose, potassium bisulfate, and allyl isothiocyanate or volatile oil of mustard.

Sinalbin, the glucoside found in white mustard, is split by myrosin into dextrose, the non-volatile mustard oil, C_7H_7ONCS , and sinapine bisulfate. The latter can be further split into sulfuric acid, choline and sinapic acid, which is the acid corresponding with syringyl alcohol.

RESINS

The natural resins are found in practically every plant, but only a few are commercial articles. If a plant is extracted with alcohol, and the

aleoholie extract is poured into water, there is precipitated a gummy mass which is largely resin. Sometimes these exude spontaneously from the plant, and often any injury to it results in such an exudation, as in the collection of turpentine. The natural resins are frequently gathered in solution in volatile oils, and they are then called oleoresins; they can be separated by distillation with steam. The resins generally are insoluble in water, but soluble in aleohol, ether, or oils. They vary considerably in consistency but are usually hard and brittle.

The resins are undoubtedly closely related to the volatile oils, which they frequently accompany in the plants. In fact, some of the simple compounds that occur in resins, such as abietic acid, can be traced directly to the terpenes or sesquiterpenes. However, in general the substances of resins are complicated and difficult to investigate, so that we know little of origin or chemical relations. For that reason, it will be impossible to give more than a rough idea of chemical composition.

In the days before Tschirch, who was the pioneer in investigation of these substances, the resins were classified into oleoresins, balsams, simple resins (true), and gum resins. The oleoresins, as we have seen, are simply solutions in oil, and the balsams are but a special class of oleoresins containing esters of cinnamic and benzoic acids. Since the gum resins are mixtures with gums, one can easily see that the classification is not one at all; the resins pure and simple are all in one class.

The grouping of Tschirch is more scientific but still leaves much to be desired. They are here classified according to the chief substance as acid, ester, or resene resins; practically every one of them contains all three of these. The resin acids are peculiar to this class of materials and, although not especially complicated, have been studied but little from the structural standpoint. Abietic acid, whose composition is known and has already been discussed, and mastic acid, $C_{20}H_{30}O_4$, are illustrations. The acids found in the resin esters are usually simple ones like benzoic, cinnamic, and salicylic acids. They are combined in the esters with colorless resinols or colored resinotannols. Examples of the former are storesinol, $C_{18}H_{30}O_3$, and benzoressinol, $C_{18}H_{28}O_2$; examples of the latter are toluresinotannol, $C_{17}H_{26}O_5$, and peruresinotannol, $C_{18}H_{28}O_5$. The resenes are indifferent substances of unknown structure; two illustrations are copalresene, $C_{25}H_{42}O_4$, and olibanoresene, $(C_{14}H_{22}O)_n$.

Rosin U.S.P. (Colophony) is the product of distilling turpentine with steam. It is chiefly abietic acid and its anhydride and is used in the manufacture of soaps and varnishes and for the preparation of rosin oil by pyrolysis for printers' ink. The other acid resins of interest are copaiba, which contains copavie acid, $C_{20}H_{30}O$, sandarae, and one or two of the copals.

In the ester class are the official balsams of peru and tolu, benzoin, storax, asafetida, and sumbul.

Most of the resins belong in the resene class, and this includes myrrh, mastic, guaiacae, and gambir, which are official. Commercially used in varnishes, lacquers, and in other ways are dammar, the copals, dragon's blood, and guni resins that are occasionally used (frankincense), and bdellium.

drugs is attributed to a resin of kind or another. This is particularly true of jalap, podophyllum, i

gamboge, and croton oil. Whether or not the presence of resins has much to do with the value of others is a question, although they are given as the potent substances in such drugs as euonymus, iris, leptandra, cotton-root hark, and kamala.

REVIEW QUESTIONS

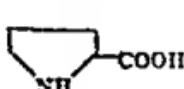
1. Define a glycoside and a glucoside.
2. What is an aglucone or genin? What structural feature have they in common?
3. Outline two methods for isolating a glycoside. Why must the enzyme be killed?
4. What enzyme in general will hydrolyze natural glycosides? alpha glycosides?
5. Outline Fischer's method for synthesizing glycosides. What was the method used for salicin?
6.
7. ruherythic acid, glycyrrhizic acid, and solanine?
8. Name four glucosides that give mandelonitrile. What is formed on further hydrolysis of the latter?
9. What are the essential differences in sinigrin and sinalbin? What is the natural enzyme for these?
10. What is the present classification of resins?
11. Name two acid resins and two resin acids.
12. Name two ester resins, three acids in the esters, two resinols, and two resino-tannols.
13. Name four official resene resins and two important commercial resins of the class.
14. Name four drugs that depend for therapeutic value on the presence of a resin.

CHAPTER XLIII

PROTEINS

AMINO ACIDS

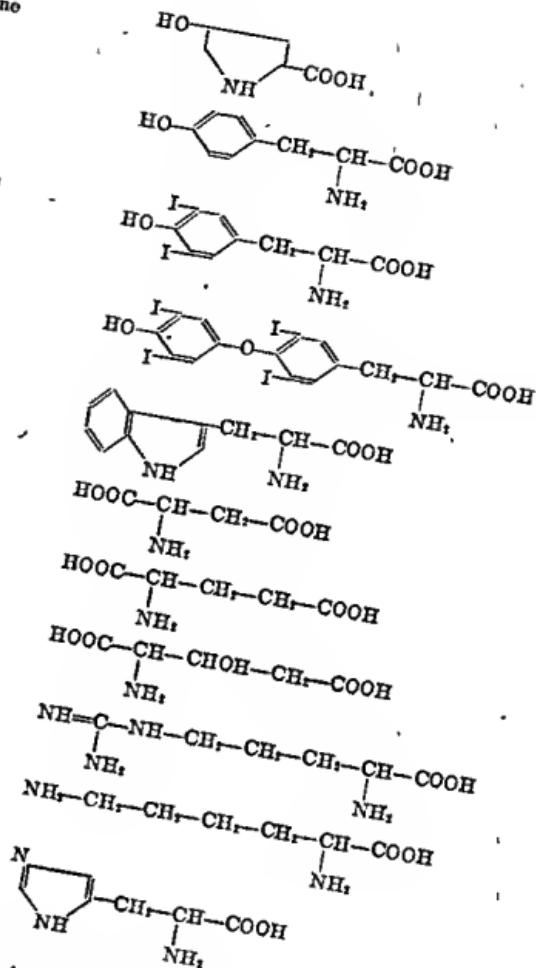
ALL simple proteins are built up by condensation from amino acids and yield only these compounds upon hydrolysis. Just as we started our study of carbohydrates with the monosaccharides, so it will be best to begin this chapter by a discussion of these amino acids. More than thirty of them have been isolated as products from all kinds of protein matter, but some of these have been obtained in only single cases, and these require confirmation. Of those generally obtainable from various proteins, we know a total of twenty-four, including two that are found nowhere except the thyroid. The student is advised to become familiar with the names and formulas of these twenty-four as given in the following list, since they play a large part in metabolism and the arbitrary names are almost universally employed.

1. Glycine	$\text{NH}_2-\text{CH}_2-\text{COOH}$
2. Alanine (dextro)	$\text{CH}_3-\text{CH}-\text{COOH}$ NH_2
3. Phenylalanine (levo)	$\text{C}_6\text{H}_5-\text{CH}_2-\text{CH}-\text{COOH}$ NH_2
4. Valine (dextro)	$(\text{CH}_3)_2\text{CH}-\text{CH}-\text{COOH}$ NH_2
5. Norleucine (dextro)	$\text{CH}_3-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}-\text{COOH}$ NH_2
6. Leucine (levo)	$\text{CH}_3-\text{CH}-\text{CH}_2-\text{CH}-\text{COOH}$ CH_3 NH_2
7. Isoleucine (dextro)	$\text{CH}_3-\text{CH}_2-\text{CH}-\text{CH}-\text{COOH}$ CH_3 NH_2
8. Threonine (levo)	$\text{CH}_3-\text{CHOH}-\text{CH}-\text{COOH}$ NH_2
9. Serine (levo)	$\text{CH}_3\text{OH}-\text{CH}-\text{COOH}$ NH_2
10. Cysteine	$\text{HS}-\text{CH}_2-\text{CH}-\text{COOH}$ NH_2
11. Cystine (levo)	$\text{HOOC}-\text{CH}-\text{CH}_2-\text{S}-\text{S}-\text{CH}_2-\text{CH}-\text{COOH}$ NH_2 NH_2
12. Methionine (levo)	$\text{CH}_3-\text{S}-\text{CH}_2-\text{CH}_2-\text{CH}-\text{COOH}$ NH_2
13. Proline (levo)	

PROTEINS

14. Hydroxyproline
(levo)15. Tyrosine
(levo)

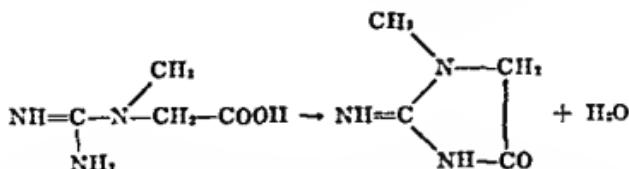
16. Iodogorgoic Acid

17. Thyroxine
(levo)18. Tryptophane
(levo)19. Aspartic Acid
(levo)20. Glutamic Acid
(dextro)21. Hydroxyglutamic Acid
(dextro)22. Arginine
(dextro)23. Lysine
(dextro)24. Histidino
(levo)

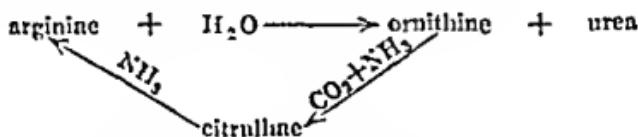
It will be noted that the majority of these contain an equal number of basic and acidic groups; this is even true of tryptophane because the cyclic nitrogen has practically no basic properties. In the last three there is a preponderance of basic groups and in the three just before them the number of acid groups is greater. If we count the phenolic hydroxyls in tyrosine, iodogorgoic acid, and thyroxine, as acid, then these should be classed with aspartic, glutamic, and hydroxyglutamic acids. It will also be noted that most of the amino acids are levo, but several of them are dextro.

A few other amino acids occur in nature but are not products from proteins. We have already noted that several have been reported as derived from proteins in single instances, but it is yet to be confirmed that they belong in our list. As example, dibydroxy-diaminobutyric acid was obtained from casein. In addition, however, a few amino acids are of great metabolic significance, although they may not be traceable to proteins. Creatine, NH₂-C(=NH)-N(CH₃)-CH₂-COOH, is present in muscular tissue as a result of normal cell activity, and it may actually be

formed from proteins. It is excreted daily in the urine as creatinine, a lactam formed by splitting out water between NH_2 and COOH ,



Ornithine, $\text{NH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}(\text{NH}_2)-\text{COOH}$, and citrulline, $\text{NH}_2-\text{CO}-\text{NH}-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}(\text{NH}_2)-\text{COOH}$, are likewise of metabolic significance. It is known, for example, that the liver through their agency forms urea from ammonia and carbon dioxide. The cycle of changes is represented by the following diagram:



The amino acids are colorless, crystalline solids that dissolve in water (except cystine, tyrosine, and tryptophane) and are insoluble in alcohol (except proline) and ether. By means of the differences of the acids and their salts in various solvents, it is possible to make a separation of mixtures obtained from proteins. They are amphoteric towards acids and bases and are generally neutral to indicators, except those that contain a preponderance of basic or acid groups. Several of them are sweet in taste. Aminoacetic Acid U.S.P. (Glycine) is the only one that does not contain an asymmetric carbon atom; they occur in the dextro or levo form but not in both. L-Cystine and L-tryptophane are official reagents.

Certain of the amino acids are dietary essentials in the form of proteins that furnish them, probably because the body can synthesize others. Those that have been placed in the essential list are lysine, histidine, leucine, isoleucine, tryptophane, phenylalanine, threonine, valine, methionine, and probably arginine.

In all compounds containing both basic and acid groups, there are undoubtedly inner salts formed. This is the case, for example, with sulfanilic acid and anthranilic acid. The amino acids are excellent illustrations of such amphoteric substances that are internally compensated; thus, glycine is $\text{NH}_3^+ - \text{CH}_2 - \text{COO}^-$. These compounds have unusually high melting points and are insoluble in alcohol and ether, behaviors that are typical of salts. Just what electrical charge is on the molecule depends on the acidity of the solution. When it has a low pH, the compound is a positive ion, $\text{NH}_3^+ - \text{CH}_2 - \text{COOH}$, and will migrate to the cathode if an electric current is passed through it. On the other hand, at high pH the compound will appear as a negative ion, $\text{NH}_2 - \text{CH}_2 - \text{COO}^-$, and will migrate to the anode. At some point between, it will be an internal, completely compensated salt, will have a zero charge, and will not migrate at all. The degree of acidity at this point, known as the isoelectric point, will vary with the individual acid, and it applies equally to all proteins.

There are several methods that can be used to synthesize the amino acids in the laboratory. The simplest one starts with the appropriate

acid, which is first chlorinated and then treated with ammonia. A second depends on the reaction of an alpha-brom ester with potassium phthalimide (Gabriel) and subsequent hydrolysis. In a third, a monosubstituted malonic ester is brominated, saponified, and then heated to drive off carbon dioxide, followed by substitution of the bromine by means of ammonia. Still another method starts with aldehyde, a metallic cyanide, and ammonium chloride. The aldehyde adds hydrogen cyanide (from hydrolysis) to give a hydroxynitrile, which reacts with ammonia from the action of the liberated base on ammonium chloride, and subsequent hydrolysis gives the amino acid.



The processes involved in these methods are well known to the student. In any method the product is racemic and must be resolved in order to get the natural acid.

The important reactions of the amino acids also involve no new principles. As amino compounds, they will neutralize acids to form salts and can be methylated and acylated as usual. They react with nitrous acid to produce hydroxyacids and nitrogen, and measurement of the gas evolved furnishes a means of estimation (Van Slyke). Aldehydes act on the amino group as we have learned and thus do away with the basic property; the carboxyl group can then be determined by acidimetry. As acids, they can neutralize bases to form salts and can be converted to various derivatives. The formation of an ester, which can be distilled, provides a convenient method for purification.

Pantothenic Acid.—This vitamin, a growth-stimulating factor of the B-complex, is found in yeast, liver, other animal tissue, and probably plants. Its constitution was determined and its synthesis was accomplished in 1940 by cooperation of chemists working with Williams and Major. By cleavage it is converted to β -alanine and a lactone, $\text{CH}_3-\overset{\text{O}}{\underset{\text{O}}{\text{C}}}(\text{CH}_3)_2-\text{CHOH}-\text{CO}$, both of which can be produced also in the

laboratory. The synthesis was made possible by combination of these and resolution of the racemic mixture, proving the structure as $\text{CH}_3\text{OH}-\text{C}(\text{CH}_3)_2-\text{CHOH}-\text{CO}-\text{NH}-\text{CH}_2-\text{CH}_2-\text{COOH}$. It is thus a substituted beta amino acid. The calcium salt is an official reagent.

PROTEINS

The proteins ("of first importance") constitute the third large class of essential foods, of which carbohydrates and fats have already been considered. They occur in all cells of both animals and plants, but whether the natural form is identical with the substances we separate from the organism is an unsettled question. None of them has ever been obtained in a pure state, although some have been crystallized.

The elementary composition shows carbon 40 to 55 per cent, hydrogen 5 to 8, oxygen 12 to 32, nitrogen 11.75 to 31.68. The great majority contain from 15 to 17.6 per cent of nitrogen, and the analyst customarily assumes an average value of 16 and so multiplies the amount of nitrogen by 100/16 or 6.25. Many contain sulfur (up to 3 per cent) and phosphorus

(up to 4 per cent). Phytovitellin, the purest protein that has been attained but which still has an ash, has C 52.43, H 7.12, O 21.80, N 18.10, S 0.55.

The molecular weights of even the simplest compounds are very high; in fact, they are so high that the ordinary cryoscopic methods are useless for determination. Several methods of attack have been more or less successful, such as estimation of the amount of sulfurous amino acids per molecule, use of the ultracentrifuge, and determination of osmotic pressure. From the results it would seem that the molecular weight has a minimum of about 17,000 and may run up to more than 6,000,000.

The proteins are usually amorphous, colorless, and insoluble in everything but water, and they have no definite melting and boiling points. Those that do dissolve in water form only a colloidal solution, which can be separated from crystalloids by the process of dialysis. They are amphoteric to reagents and are mostly neutral to indicators, although some react slightly because of a preponderance of acid or basic amino acids. At the isoelectric point the solubility is lowest and precipitation can occur in concentrated solution. By the addition of much inorganic salt, such as ammonium or magnesium sulfate, practically all soluble proteins are precipitated, to be redissolved on great dilution.

With very dilute copper sulfate and alkali, they form a violet color (biuret reaction), also given by other compounds that contain amide groups close together. With acid mercuric nitrate solution (Millon's reagent), they yield a red color or precipitate, which is given by tyrosine and phenolic compounds generally. With nitric acid they produce a yellow color by nitration of benzene nuclei (xanthoproteic reaction); the stains on skin by nitric acid are of this type. Due to the presence of tryptophane, proteins give a violet ring with acetic and sulfuric acids (Adam-Kiewicz) or with glyoxylic acid (Hopkins-Cole), and they also give a violet color with formaldehyde, hydrochloric acid, and a trace of ferric iron (Leach). All amino acids and proteins yield with ninhydrin (triketohydrindene hydrate) a blue-violet color. Many other color reactions of a similar nature are used for identifying.

The universally adopted classification of proteins divides them into three groups: simple, conjugated, and derived. The simple proteins hydrolyze entirely to amino acids and are further divided on the basis of solubility into seven classes: protamines, histones, albumins, globulins, prolamines, glutelins, and alburnoids. The protamines and histones are basic, soluble in water, and not coagulated by heat, the histones being insoluble in ammonia. They are chiefly of academic interest, because the protamines are obtained only from the sperm of fish, and the histones are comparatively rare.

Albumins are soluble in water and are coagulated by heating to 65° to 75°. They occur very commonly in both plants and animals, where they constitute a large share of the protoplasm. The best common illustration is the white of an egg or egg albumin, and others are serum albumin of blood.

T

are

of egg, almandin of almond, and myosin of muscle. They are insoluble in water but soluble in very dilute salt solutions, from which they are

cipitated on dialysis. They are coagulated by heat, usually at a lower temperature than albumins; for example, myosin coagulates at 56°.

The prolamines are insoluble in water or alcohol but do dissolve in 70 to 80 per cent alcohol. They occur only in vegetable matter, some examples being gliadin of wheat, zein of corn, and hordein of barley.

The glutelins also occur only in vegetable matter. They are insoluble in water, alcohol, or salts, but will dissolve in very dilute acids or alkalies. An illustration is the glutenin of wheat, which with gliadin makes up what is known as gluten.

The albuminoids are insoluble in all solvents, although they can be dissolved by H_2O_2 : H_2O_2 : H_2O_2 them. Examples are keratin of hair, elastin of skin, collagen of connective tissue, and spongin. H_2O_2 from collagen by boiling with water and is probably of much lower molecular weight. The structure of these albuminoids has been investigated by means of X-ray diffraction, similar to the method used in determining crystal lattice, and it has been found that they contain a definite structural pattern of long chains, as contrasted with the probable three-dimensional molecules of other proteins.

The conjugated proteins contain some other substance combined with the simple protein, and this non-protein portion of the molecule is called a prosthetic group. In some cases the protein may be the smaller part of the whole molecule. These conjugated compounds are classified according to the character of the prosthetic group. Some of them are chromoproteins like hemoglobin, glycoproteins such as mucin of the mucous secretions, lecithoproteins, phosphoproteins like casein, and especially nucleoproteins which occur very widely and are rich in phosphorus. We have already seen that the nucleic acids, the prosthetic group of nucleoproteins, are hydrolyzed to pentoses, phosphoric acid, and pyrimidine derivatives. The character of linking between prosthetic group and protein is not always the same, because in many cases it is impossible to separate the former without decomposing the latter.

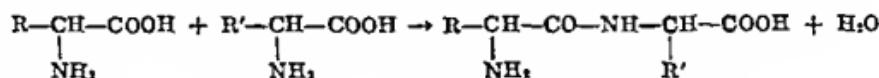
The derived proteins, meaning those formed by chemical change, are arbitrarily divided into primary and secondary, depending on the profoundness of that change. One of the striking characteristics of all soluble proteins is the ease with which such alterations are brought about. The primary compounds are formed by mild action or denaturing and, if this is very mild, it is sometimes possible to restore the protein, although generally the process is irreversible. The precipitation by means of heavy metallic salts, tannic acid, picric acid, etc., and coagulation by heat or reagents are usually of the irreversible type. The proteins, metaproteins, and coagulated proteins are classes of primary derivatives.

The secondary derived proteins represent more profound change involving hydrolysis, and they are divided into proteoses and peptones. They are intermediate between simple proteins and amino acids and, although less complex than the former, yet have a high molecular weight. Both classes are soluble in water and not coagulated by heat, but the proteoses are distinguished by being precipitated when their solution is saturated with ammonium sulfate. Meat extract contains much proteose and some peptone.

Along with these two classes of secondary derived proteins are usually placed the synthetic polypeptides, which have much smaller molecules.

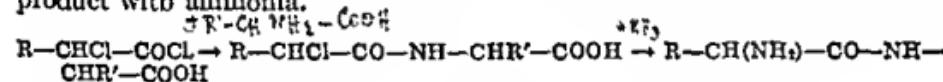
The recombination of amino acids to produce proteins has, of course, been the dream of chemists ever since the discovery of protein hydrolysis, and many have tried to accomplish it. The most successful was Emil Fischer, who put together as many as eighteen molecules of the amino acids, fifteen of glycine and three of leucine. These synthesized molecules are called dipeptides, tripeptides, etc., and in general polypeptides. The particular compound of eighteen molecules of amino acids had a molecular weight of over 1200, was soluble in water to form a colloidal solution, and gave several of the protein reactions, including hydrolysis by proteolytic enzymes. This would seem to indicate that the manner of linking that Fischer utilized is the one found naturally.

The molecules of amino acid are joined to each other just as if dehydration had taken place between NH_2 of one and COOH of the other.



Indeed, a dipeptide can be made in about this way, but combining of another molecule by the same process is not feasible, in spite of the fact that the dipeptide has yet an NH_2 and a COOII .

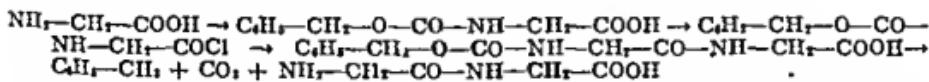
The methods actually used for such syntheses are quite varied, and it is not practical to describe them all here. One used by Fischer was to combine an alphachloroacid chloride with an amino acid and treat the product with ammonia.



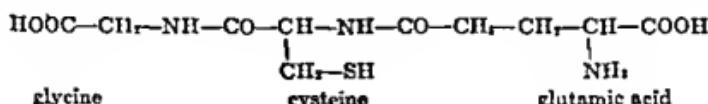
If chlorides of all amino acids could be made directly, there would be little trouble in building up the molecules. In order to keep the amino and other groups except the carboxyl from reacting, one can introduce protecting groups, such as acetyl for the amino. The difficulty then is to remove the protecting radical without disrupting the synthesized molecule, because this usually involves hydrolysis. A more recent method (Bergmann) is to protect the amino with carbobenzyloxy, $C_6H_5-CH_2-O-CO-$, which can be removed by catalytic reduction. This group is introduced by benzylchloroformate, made from benzyl alcohol and phosgene.



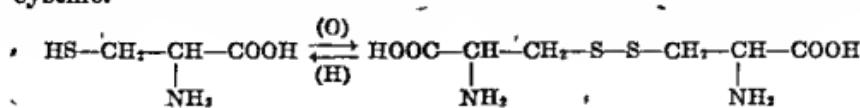
The synthesis is illustrated by glycine to give glycylglycine.



Glutathione is an important tripeptide that occurs naturally and undoubtedly plays a significant rôle in oxidation and reduction reactions of the metabolism. Its molecule is built up from cysteine, bound on the one hand to glycine, on the other to glutamic acid.



The constitution as given has been demonstrated by synthesis. The rôle in oxidation and reduction is probably similar to the change from cysteine to cystine.



REVIEW QUESTIONS

1. Name ten important amino acids and give the formulas. What three are basic and what three are acidic?
2. Write the formulas of creatine and creatinine. Where are they found?
3. Show how ornithine and citrulline are used by the liver to make arginine and then urea.
4. What is the evidence that amino acids are inner salts? What is meant by the isoelectric point?
5. State four methods for synthesizing amino acids and write equations.
6. How could a water solution of a protein be separated from a crystalloid?
7. Describe the following protein reactions: biuret, Millon, xanthoproteic, Adamkiewicz, Hopkins-Cole, ninhydrin.
8. Name the five common classes of simple proteins, and state the source, solubility, and a representative of each.
9. What is the source of gelatin?
10. What is a conjugated protein? Name three classes and give an illustration of each.
11. What is meant by a primary derived protein? Illustrate three ways in which they can be made.
12. What are the proteoses and peptones? What is the solubility in water and how does it probably act?

Write equations.
metabolism? How

CHAPTER XLIV

ENZYMES

ENZYMES are natural organic catalysts, so necessary to the processes that must go on in the metabolism of plants and animals. They are usually distinguished sharply from organized fermentations, which are living organisms that produce the enzymes. Thus, yeast is a ferment that produces zymase, but the latter when separated from the yeast is as efficiently capable of accelerating fermentation as if it were in the organism. In other words, enzymes are entirely independent of the body that produces them and are chemical entities.

They are colloidal substances of high molecular weight and probably protein in character. Like all colloidal matter, they are very liable to absorb other compounds and are thus rendered very resistant to purification or isolation. Up to a few years ago they were used either in the form of organized fermentations like yeast or as aqueous extracts obtained by crushing and grinding the plant or animal material with water or salt solution. Later it was found that alcohol, acetone, and various salts could sometimes be used to precipitate an active material, thus giving the enzyme in a solid state as powder.

A large step forward was made when some of these compounds were isolated in a more or less pure state and crystallized. In at least a half-dozen cases it has been found possible to precipitate, dissolve, evaporate, and otherwise purify, without detracting from the activity, and finally convert to crystals. A study of the properties of these has inevitably led to the conclusion that they are proteins. Although some biochemists are still doubtful, most of the available evidence is strongly for the decision that all enzymes are proteins with special structure for some particular function. Just what this peculiar nature is, which allows an enzyme to accomplish a given purpose, must for the present remain obscure, although a number of unprovable theories have been advanced.

Like all true proteins that are soluble, the enzymes are easily inactivated or destroyed by conditions or reagents, a denaturing process. All of them lose their activity when their solutions are heated for a short time above 80° to 90°, although in the dry state they may not be affected by this temperature for a reasonable length of time. Ultraviolet light, or even ordinary sunlight for a sufficient period, is able to inhibit their power and sometimes destroy them. The loss of activity is likewise brought about by various reagents, such as strong acids and bases, formaldehyde, oxidizing agents, and salts of heavy metals. On the other hand, a few substances that kill ferments have no effect on the enzymes and can be used to preserve them; chloroform and thymol are commonly employed for this purpose. Any inactivation is almost always permanent, although removal of the detrimental reagent if mild will occasionally restore the power.

The enzymes conform strictly to the usual definition of a catalytic agent, but in some ways they are unique. The speed of the reaction is altered, either decreased or increased, in proportion to the amount of

enzyme present. Theoretically a minute amount can convert any quantity of the reacting substance (substrate), providing there is enough time, but practically some is always destroyed at the same time, and often the accumulation of products tends to inhibit the activity. The enzyme itself does not seem to take part in the reaction, although it would appear reasonable to suppose that it must be changed and the change reversed many times while the reaction is going on. They often will promote the reverse reaction; thus, those that decompose compounds like the carbohydrates can often be used to build up the same compound. They differ from other catalysts in that their power is entirely specific, though it may be limited to common groups of substances rather than to a single one. They also differ in being able to induce reactions, a condition that is probably essential in the organism, where changes of temperature and other tools of the chemist are lacking. Their action is greatly influenced by small changes in temperature and hydrogen-ion concentration, and for each enzyme there is an optimum. Generally the pH range is from 4 to 8 and that of the temperature is from just above that of the room up to about 55°. Finally some will not act at all unless there is present a particular substance called a co-enzyme; for example, ionic calcium is necessary for the action of rennin on milk, although the reason is unknown.

In the natural state many enzymes exist in a masked form, and in these cases a releasing agent is necessary. This is particularly true of the blood-clotting thrombin, but we might also note that pepsin is in the form of pepsinogen. In nature, too, the enzyme is frequently accompanied by an agent that acts in the opposite direction, a sort of a damper that works in an unknown way. Indeed, it has been postulated that all metabolic processes are controlled by the activity of two sets of agents whose power is antagonistic.

We will not attempt to describe all of the many enzymes that have been isolated or characterized, but will confine our attention to a few of the more important ones. The large majority are hydrolases, catalyzing hydrolytic actions, a number are specific for oxidations and reductions, and a few have some special function. The names of all end in -ase, except that those known for a long time have retained the older names like pepsin.

Proteolytic (proteases).—Pepsin N.F., occurring in the stomach of animals, acts upon proteins of all kinds to hydrolyze them as far as proteose and peptone. The powder will keep fairly well in the dry state, but decomposes rapidly if moist or in solution, especially at somewhat elevated temperatures. Alkalies decompose it, and other proteolytic enzymes will digest it at the proper pH. The official material must convert 3000 to 3500 times its weight of coagulated egg albumin to soluble form in two and one-half hours. Pepsin has been obtained in the crystalline state.

Pancreatin U.S.P. is a dry powder representing the enzymes found in the pancreatic juice, and it is presumed to contain amyllospin, trypsin, and steapsin. Trypsin, which hydrolyzes proteins as far as peptides and amino acids, is also quite labile, and old samples of pancreatin frequently contain none. It operates in weakly alkaline media and is easily destroyed in acid solution by reagents or pepsin. The official pancreatin must hydrolyze 25 times its weight of casein in five minutes. Trypsin is claimed to be a mixture of enzymes but has been crystallized. The amyllospin hydro-

lyzes starch to soluble carbohydrates and is required to convert 25 times as much as the weight of sample taken in one hour.

Rennin N.F., obtained from the glandular layer of the calf's stomach, has the power of coagulating casein in milk and is required to convert about 25,000 times its own weight of milk in the same time as required by a standard rennin. Fresh preparations have been known to act upon more than a thousand times this amount. Rennin is the active ingredient in commercial junket tablets.

Papain, obtained from the skin of the paw paw, *Carica papaya*, is a proteolytic enzyme that acts in pH between 4 and 8 and at 65° to 90°. It is becoming increasingly important as a tenderizer of meat; the United States imported 27 tons in 1932, 90 tons in 1937, and 112 tons in 1938. Most of it comes from Ceylon, although the fruit is grown in our southern states.

Amylolytic (carbohydrases).—These hydrolyze carbohydrates to lower forms, sometimes only to soluble forms and often to monosaccharides. The glycoside enzymes may be included.

Malt, the partly and artificially germinated grain of barley, contains diastase or amylase, which will convert starch to maltose. Extract of Malt U.S.P. is required to change not less than 5 times its weight of starch to water-soluble form in thirty minutes. Commercial diastase is employed to predigest carbohydrates in the manufacture of breakfast foods.

Maltase, which is found in yeast, malt, and the human intestines, primarily converts maltose to dextrose, but it also acts on other alpha glucosides. It can be used to synthesize maltose and isomaltose from dextrose. The fermentation of maltose by yeast proceeds readily because of the presence of this enzyme.

Invertase (sucrase or saccharase), found in yeast, intestinal juices, and the leaves of many plants, converts sucrose to dextrose and levulose. Lactase of the intestines acts in a similar way on lactose.

Ptyalin or salivary diastase, which is found in the salivary secretions of animals and men, changes starch and dextrins to maltose.

Emulsin, which is very widely distributed in nature and is usually obtained from the bitter almond, will hydrolyze amygdalin and many other natural glucosides. Since it acts on synthetic beta, but not alpha, glucosides, the assumption is reasonably made that natural compounds are beta.

Myrosin, another of the numerous glycosidal enzymes, is found in both white and black mustard, chiefly in the former. It will hydrolyze either sinigrin or sinalbin and will also act on a few other like compounds in other plants.

Esterases.—The lipases, which partly or completely change fats to glycerin and fatty acids, are found in all animal digestive systems. The steapsin of pancreatic juice has already been noted. There are in both plants and animals other esterases, as for example, the phosphatase of the intestine, which converts nucleotides to nucleosides and phosphoric acid.

Urease, obtained from the soy bean, is a common laboratory reagent for converting urea to ammonia by hydrolysis. It was the first of the enzymes to be crystallized. Arginase of the liver changes arginine to ornithine and urea.

Oxidizing.—Zymase of yeast was one of the first enzymes to be studied, since it is essential in the age-old process of fermenting sugars. It splits the monosaccharides by oxidation and then reduces a portion to ethyl alcohol. One would conclude that it is probably a mixture of enzymes.

Others of this class are the oxidases that are universally found in all kinds of plants; catalases, which are present in practically all vegetable and animal cells and have the power to decompose hydrogen peroxide; mutase, which converts aldehydes to alcohol and acid; and the aldehyde-reductase of milk, whose reaction in decolorizing methylene blue and formaldehyde is a test for raw milk.

One of the most interesting of these enzymes is the thrombin of blood. The entire set of conditions for coagulation of blood is not quite clear, but the essential phase is change of the protein fibrinogen to a coagulated fibrin. The thrombin, which brings this about, exists in the blood as prothrombin, apparently in combination with an unknown material that inhibits its change to thrombin. When the tissue is lacerated, a material is set free from certain cells (thromboplastin) to withdraw this inhibiting substance. The released prothrombin is converted by calcium salts to thrombin which brings about the coagulation. Whatever the mechanism, the clotting of blood necessitates at least four factors: calcium salts, the tissue substance called thromboplastin, thrombin or prothrombin, and fibrinogen.

REVIEW QUESTIONS

1. How are the enzymes prepared from natural materials?
2. In what way can they be inactivated? Can this be reversed?
3. What is meant by substrate? co-enzyme?
4. In what respects do enzymes differ from other catalytic agents?
5. What are the source and function of pepsin? How is it assayed?
6. What enzymes are contained in pancreatin? What is the function of each? How is pancreatin assayed?
7. What are the source and function of rennin? How is it assayed? What is junket?
8. What is papain and what reaction does it catalyze?
9. Where is diastase found and what is its function?
10. Upon what glucosides does maltase act? Where is it found?
11. Give the source and function of each: ptyalin, emulsin, myrosin, lipases, phosphatase, urease, zymase, catalase, mutase, and aldehyde-reductase.
12. Describe the conditions necessary for the clotting of blood. What four factors are needed?

A RECOMMENDED LIST FOR SUPPLEMENTAL READING

This list is not intended to be complete nor to include every important book; it is designed only as suggestive for study and reference.

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